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Mason, M ; Laperriere, N ; Wick, W ; Reardon, D A ; Malmstrom, A ; Hovey, E ; Weller, M ; Perry, J R

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Glioblastoma in the Elderly: Making Sense of the Evidence

Matthew Mason[1], Normand Laperriere[1], Wolfgang Wick[2], David A. Reardon[3], Annika Malmstrom[4], Elizabeth Hovey[5], Michael Weller[6] & James R Perry[7]

1) Department of Radiation Oncology, Princess Margaret Cancer Centre, University of Toronto, 610 University Avenue, Toronto, ON, M5T 2M9 Canada

2) Neurology Clinic & National Center for Tumor Disease and Neurology Clinic, Heidelberg University Medical Center & DKFZ, Heidelberg, Germany.

3) Center for Neuro-Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, Dana 2134, Boston, MA 02215-5450 USA

4) Department of Advanced Home Care and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

5) Department of Medical Oncology, Prince of Wales Hospital, Barker Street, Randwick NSW 2031 Australia

6) Department of Neurology, University Hospital Zurich, Frauenklinikstrasse 26, CH-8091 Zürich, Switzerland

7) Division of Neurology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, M4N 3M5 Canada

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Corresponding Author:
James Perry MD, FRCPC
Division of Neurology, Sunnybrook Health Sciences and Odette Cancer Centre,
A402, 2075 Bayview Avenue
University of Toronto, Toronto, Ontario, Canada
M4N 3M5
Ph: 416 480 4766
Fax: 416 480 5054
Email: James.Perry@sunnybrook.ca

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Abstract:

Glioblastoma is a highly malignant neoplasm, notorious for its poor prognosis. The median age of diagnosis is 64 years, with an increasing number of patients diagnosed over the age of seventy. Managing elderly patients with this condition is challenging. Management pathways may include surgery, radiotherapy (RT), chemotherapy and best supportive care (BSC). Many clinical trials in oncology exclude elderly patients, including some of those for malignant brain tumors leaving less evidence to guide treatment in the these patients. Recent advances in molecular diagnostics and biomarkers, such as 06-methylguanine-DNA-methyltransferase (*MGMT)* promoter methylation status, may help guide optimal treatment selection. Focusing on available randomized data, this review provides a practical overview of the evidence for the treatment of newly diagnosed glioblastoma in the elderly including management recommendations.

Keywords: Elderly, glioblastoma, surgery, radiotherapy, chemotherapy

Convention is to define the 'elderly' population as exceeding a specified chronological age which varies with temporal, geographical, social and cultural factors. Managing elderly patients can be challenging; medical comorbidities, multiple concomitant medications, and increasing fragility of health alter drug efficacy and the magnitude and spectrum of adverse effects related to treatment. With age, the natural insidious change of physiology and constitution affects pharmacokinetic processes with regards to absorption, metabolism, distribution and drug clearance.[1] Many clinical trials in oncology exclude elderly patients, including some of those for malignant brain tumors; as such there is less evidence to guide treatment in the elderly cohort. This review provides a practical overview of the evidence for the treatment of newly diagnosed glioblastoma in the elderly.

Epidemiology

Glioblastoma is a highly malignant neoplasm, notorious for its poor prognosis. The Central Brain Tumour Registry of the United States (CBTRUS) statistical report, which collates epidemiological data from over 50 state cancer registries, identified 112,458 malignant primary brain and central nervous system (CNS) tumors between 2006 and 2010 of which 45.2% were glioblastomas.[2] A median age of 64 at diagnosis and an average age-adjusted incidence rate per of 3·19 (3·16-3·21) per 100,000 were reported. Stratification by age detected an increase in incidence with age, and the peak rate of 14·93 in the 75-84 age range. Of note is the marked decrease in survival with advancing age (table 1). The 1-year and 2-year relative survival rates of

40·7% and 14·2% for patients aged 55-64 falls to 9·2% and 2·6% for patients aged 75 or older. An Ontario (Canada) population-based cohort study of all patients diagnosed with glioblastoma between 1982 and 1994 found poorer survival with respect to each increasing decade of age (Figure 1 courtesy of Paszat et. al. Unpublished 1999). Whether this poorer survival is a reflection of differing provisions of care based on chronological age or reflects more aggressive tumor biology, or both, is presently unclear.

The histologic hallmarks of glioblastoma, as defined by the World Health Organization (WHO), include cellular polymorphism, nuclear atypia, a high mitotic index, microvascular proliferation and necrosis.[3] With the emergence of personalized medicine, molecular diagnostics are increasingly used to improve the treatment and survival associated with glioblastoma. Prognostic biomarkers such as TP53 mutation, 1p deletion, cyclin dependent kinase (CDK) N2A/p16 deletion and epidermal growth factor receptor (EGFR) amplification vary with age[4]. In a histological review of 140 patients, *TP53* mutations and *EGFR* amplification had differing prognostic significance when stratifying by age, with TP53 mutations being positively prognostic for younger patients and negative for older patients (<70yrs 0.84; 95% CI 0.49 –1.42 versus >70yrs HR 7.54; 95% CI 2.38–23.87)[4]. Conversely *EGFR* amplification in the context of older patients was positively prognostic yet in younger patients it was negatively prognostic.[4]

More recently gene expression-based molecular analysis has been utilized to categorize glioblastoma into subtypes including proneural, neural, classical and mesenchymal subtypes.[5] Lee et al. performed a meta-analysis which substantiated the presence of these subtypes, as identified by genetic signature and suggested that the prognostic effect of age may in fact be a reflection of the differing prevalence of specific subtypes at differing ages; for example the

proneural subtype appears to occur more often in younger patients and is associated with longer survival.[6] Presently these markers do not have a defined role in clinical practice with regards to daily management decisions and remain under investigation. Of note, positive prognostic biomarkers, like mutations of *isocitrate dehydrogenase (IDH)* are virtually absent in glioblastoma of the elderly; similarly the general DNA methylation levels in the tumor tissue seem to be low. Despite this the frequency of *O6-Methylguanine-DNA methyltransferase (MGMT)* promoter methylation, itself an important positive predictive marker, does not vary with age.[7]

Surgery

In younger patients, maximal safe resection is advocated with the intent of preserving neurological function, providing maximal tissue for molecular profiling, and improving overall survival. Analysis of the extent of surgery in Radiation Therapy Oncology Group (RTOG) randomised trials, found significant improvement in survival with partial/total resection versus biopsy alone.[8] Review of an unselected population of 345 newly diagnosed glioblastoma patients from the German Glioma Network (GGN) demonstrated gross tumour resection to be associated with superior overall survival (OS) (median 17·1 months) compared to incomplete resection (median 11·7 months) and biopsy alone (median 8·7 months).[9] A multivariate analysis of 416 glioblastoma patients treated at a single institution between 1993 and 1999 reported resections of tumour volume in the order of 98% or greater to be associated with significant survival advantage (median survival 13 months, 95% CI 11·4–14·6 months versus 8·8 months (95% CI 7·4–10·2 months; $p < 0{\cdot}0001$).[10]

There is one randomized trial pertaining to surgical intervention, including elderly patients with glioblastoma. This small study of 30 patients assessed the role of debulking surgery compared to biopsy alone.[11] Patients aged 65 or older with KPS >60 were randomized to open craniotomy and resection [14 patients with a median age of 70 (66-80)] or stereotactic biopsy [16 patients with a median of age 72 (67 -79)]. Surgical resection resulted in superior overall survival (171 days (95% CI 146–278) vs. 85 days (95% CI 55–157) p = 0·0346). More recently, a case-control study with a subgroup analysis of 52 patients aged 70 or over found a median survival of 4·5 months and 3 months for surgical resection and needle biopsy respectively (p = 0·03).[12] Perhaps the most relevant trial for the topic is the Neuro-oncology Working Group of the German Cancer Society NOA-08 study which found extent of surgery to be an independent prognostic factor for overall survival among glioblastoma patients 65 years and older.[13] Furthermore, multivariate analysis of all patients (n=342) participating in the Nordic trial of standard vs. hypofractionated radiotherapy vs. chemotherapy alone in newly diagnosed glioblastoma patients 65 years of age or older also demonstrated a survival benefit favoring surgery over biopsy alone (biopsy versus resection HR 1·50 (1·17 -1·92) p =0·001).[14]

Standard post-operative management for newly diagnosed glioblastoma

The European Organisation for Research and Treatment of Cancer (EORTC) 26981-22981/National Cancer Institute of Canada Clinical Trials Group (NCIC) CE.3 randomised phase III trial assessed the addition of temozolomide (TMZ) to radiotherapy (RT) in the concomitant and sequential adjuvant setting in glioblastoma patients aged 18-70.[15] Median age was 56 (range 19-71) and the selected population required Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. The addition of TMZ resulted in a median survival benefit of 2·5

months; 14·6 months (95% CI 13·2- 16·8) compared with 12·1 months (95%CI 11·2 -13·0) for radiotherapy alone. The 5-year analysis of this trial confirmed a persisting advantage and this has become the standard of care post-surgical resection for patients less than 70 years of age and of appropriate performance status.[16] In a recent review Laperriere et. al. noted that subgroup analysis of this trial demonstrated a trend to benefit in the more elderly subgroups, albeit with a less impressive hazard ratio and without reaching statistical significance. Specifically, there was diminishing benefit of combined treatment with increasing age (61-65 years: HR 0.64 p = 0.096 and 66–70 years: HR = 0·78 p = 0·34) compared to the overall group (HR 0·6, 95%CI 0·5-0·7; p<0·0001).[17] This may reflect less robust effects of the combined approach in the elderly or may be due to lower statistical power in the subgroup analysis.

Radiation for elderly patients

Randomized trials have long demonstrated a survival benefit from post-operative radiotherapy in the management of glioblastoma and more recently several trials have focused on the elderly. The French ANOCEF group found a median survival benefit of 12.2 weeks in favour of RT plus best supportive care (BSC) versus BSC alone.[18] Patients aged 70 or older with a KPS >70 and a diagnosis of glioblastoma or anaplastic astrocytoma were randomized postoperatively to receive BSC [(42 patients (median age 73; range 70-85)] or BSC and 50 Gy in 1.8 Gy fractions to a clinical target volume (CTV) consisting of enhancing tumour with a 2cm margin [(39 patients (median age 75; range 70-84)]. Overall survival was 16·9 (95% CI, 13·4 to 21·4) and 29·1 weeks (95% CI, 25·4 to 34·9) respectively. No significant difference was detected with regards to quality of life; however, Health Related Quality of Life (HRQoL) assessments were

incomplete. Cox proportional hazard modelling revealed that extent of surgery was associated with increased survival.

Scott et al. performed a large retrospective review of elderly glioblastoma patients diagnosed between 1993 and 2005.[19] The study sample of 2836 patients identified from the Surveillance, Epidemiology, and End Results (SEER) registry database had a median age of 76·9 years (range 71·0–98·0). Kaplan-Meier analysis revealed median cancer-specific survivals of 8 months for patients undergoing both surgery and postoperative radiotherapy, 4 months for radiation alone, 3 months for surgery alone and 2 months for neither surgery nor radiotherapy (log rank p<0·001). Multivariate analysis suggested radiotherapy significantly increased cancer-specific survival after adjusting for tumour size, tumour location, surgery and patient demographics with a hazard ratio (HR) of 0·43 (95% CI, 0·38–0·49). [19]

The biological effect of radiation on tumour and normal tissues is dependent upon the provision of dose over time as well as intrinsic radio-sensitivity (α) and repair capability (ß). Glioblastoma has an alpha-beta ratio (α/ ß) = 8Gy (5·0–10·8)[20] which is in the range of most tumours, while the alpha-beta ratio is approximately 2 for the normal central nervous system. As a result of this difference, hypofractionation reduces overall treatment time and may minimize the potential for tumor cell repopulation and provides a practical convenience for an elderly frail population. Roa et. al. randomized patients aged 60 or older to radiotherapy given as 60Gy in 30 fractions (47 patients, mean age 72.4 yrs, SD 5·4) or a hypofractionated regimen of 40Gy in 15 fractions (48 patients, mean 71·0 yrs, SD 5·5).[21] While this study was not sufficiently powered to conclude equivalence of these two fractionation schedules it suggested no significant differences in OS [median 5.1 months for the standard RT arm versus 5·6 months for the shorter course (log rank p = 0·57)], survival at 6 months (44·7% standard RT versus 41·7% hypofractionated RT), or

HRQoL. More patients required an increase of corticosteroid dose following the standard radiotherapy schedule compared to the hypofractionated course (p= 0·02).

The Nordic trial incorporated a different hypofractionated radiotherapy schedule.[14] There were 3 treatment arms including standard radiotherapy of 60Gy in 30 fractions, hypofractionated radiotherapy of 34Gy in 10 fractions or temozolomide 200mg/m2 days 1-5 every 28 days for up to 6 cycles. Standard radiotherapy (60Gy/30) was not routinely offered to elderly patients in some study sites so randomization between just the hypofractionated radiotherapy and temozolomide arms was permitted. Two hundred and ninety one glioblastoma patients (initially aged 60 years or older then in view of EORTC 26981-22981/NCIC-CTG CE.3 the age eligibility was adjusted so that patients 60-65 years old fit for combined treatment were excluded) were randomized to standard radiotherapy (n=100), hypofractionated radiotherapy (n=98) or temozolomide alone (n=93). A further 51 patients were randomized to either hypofractionated radiotherapy (n=25) or TMZ (n=26) by those centers that did not offer 60Gy in 30 fractions as their standard care.

The median age was 70 for both the hypofractionated and the standard radiotherapy groups. Median survival in the hypofractionated group was increased by 1·5 months compared to standard radiation in the three-arm comparison. Interestingly, on stratification by age, the advantage of hypofractionated radiation appeared better in patients over the age of 70 (7·0 (5·2–8·8) versus 5·2 (4·0–6·3) months). Treatment completion according to protocol was more frequent with the hypofractionated schedule (95% versus 72%). Salvage treatment was received for a similar proportion of patients in both groups while reported toxicity was not different between groups.

Temozolomide and O-6-methylguanine-DNA methyltransferase

The alkylating agent TMZ has activity in glioblastoma, and in combination with radiotherapy followed sequentially by a 6 month maintenance course represents the current standard of care for many patients. The mechanism of anti-tumour activity is believed to arise through methylation of DNA at the O-6 position of guanine by monomethyl-triazeno-imidazole-carboxyamide (MTIC), a non-enzymatic chemical degradation product of temozolomide.[22]

MGMT is a DNA repair protein implicated in resistance to alkylating agents.[23] Methylation of the *MGMT* promoter, located at 10q26, leads to suppression of *MGMT* gene expression and an increased likelihood of clinical benefit.[23-25] Hegi et al. assessed the *MGMT* promoter methylation status of patients randomized in the EORTC trial 26981/ NCIC CE.3 trial.[25] Regardless of treatment arm, OS was longer in patients with *MGMT* promoter methylation; 18.2 months compared with 12.2 months [HR for death 0·45 (95% CI 0·32 - 0·61)]. The magnitude of this effect was more substantial for patients receiving TMZ compared with those receiving radiation alone (P=0·007 vs. P=0·06, log-rank test). Of note, the majority of patients allocated to radiotherapy alone received alkylating agent chemotherapy as salvage treatment further supporting the use of concomitant therapy 'upfront' in newly diagnosed patients.[25] The prognostic significance of *MGMT* promoter methylation status was prospectively corroborated in the RTOG 0525 randomized study of TMZ dose density in the adjuvant setting. In this study, dose-dense TMZ (n=422) failed to demonstrate a survival advantage over standard dosing (n=411).[26] The absence of a TMZ-free control arm did not allow distinction between prognostic and predictive properties.

For elderly patients not suitable for the combined modality approach, recent evidence supports consideration of TMZ alone particularly for tumors harbouring *MGMT* promoter methylation.[27] Temozolomide alone was assessed in the Nordic study,[14] which found longer survival for both TMZ alone and hypofractionated radiotherapy over standard radiotherapy in patients older than 65 years of age. Comparison of TMZ and hypofractionated radiotherapy revealed no significant difference in overall survival (7·4 versus 8·4 months HR 0·82 95%CI 0·63-1·06). In the head to head comparison of TMZ versus hypofractionated radiation, 36% of the TMZ recipients had subsequent radiation and 29% of the hypofractionated group had salvage chemotherapy. *MGMT* promoter methylation status was available in 258 (75%) of 342 patients. Patients with *MGMT* promoter methylated tumors receiving TMZ survived 2.9 months longer than those with unmethylated tumors (HR 0·56, 95% CI 0·34-0·93, p=0·02). No survival advantage was identified based on *MGMT* promoter methylation status within the cohort receiving radiation (HR 0·97, 95% CI 0·69-1·38, p=0·81). Although the intent for the TMZ group was to complete six cycles, at least two cycles were administered to 86% of patients, and only 34% completed all six cycles. Haematological toxicity as well as nausea and vomiting were more frequent as would be expected in the TMZ cohort. In addition, a treatment-related death involving thrombocytopenia highlights that prescribing chemotherapy is not without the potential for serious toxicity.

In the NOA-08 study,[13] 192 patients received TMZ (1 week on, 1 week off schedule 100 mg/m2 days 1–7) and 178 patients received 60Gy radiotherapy alone over 6–7 weeks to the gross tumour volume (GTV) + 2 centimeters. Median overall survival was similar for the two treatment arms: 8·6 months in the TMZ group and 9·6 months in the radiotherapy group (HR

1·09, 95% CI 0·84–1·42, p non-inferiority=0·033). *MGMT* promoter methylation status was available in 55% of patients receiving TMZ and 57% of patients receiving radiation with a predictive benefit seen for patients receiving the alkylating agent in the context of *MGMT* promoter methylated tumors. Hematological toxicity, abnormal liver function tests, infections and thromboembolic events were more prevalent in the TMZ group.

These trials found that *MGMT* promoter methylation is a predictive biomarker of benefit from TMZ, but not radiotherapy. The randomized international NCIC/EORTC/TROG study, which completed accrual in September 2013 (JP, personal communication), aims to address the potential benefit of combining short course radiotherapy (40Gy in 15 fractions) with concurrent and adjuvant TMZ in patients over 65 years who have had prior surgery/biopsy at diagnosis and are not deemed suitable for the standard radiotherapy regimen of 60Gy.[28] MGMT status will be assessed in this study.

A phase 2 ANOCEF study suggests that older age and poor KPS should not preclude the use of TMZ alone.[29] This was a non-randomized study which recruited 70 patients with a median age of 77 (range 70-87) and a median KPS of 60 (range 30-60). Intriguingly this study found an improvement of KPS in excess of 10 for 23 (33%) of treated patients with 18 (26%) having a rise to 70 or more. A maximum of 12 cycles of TMZ was planned however the median number of cycles received was only 2 with 20% and 24% of patients having dose delays and dose reductions for hematological toxicity respectively. Grade 3 or 4 hematological toxicities were not insignificant with 13% experiencing grade 3-4 neutropenia and 14% grade 3-4 thrombocytopenia. No deaths were attributed to treatment. Although only 44% of patients were able to have tumor material assessed for *MGMT* promoter methylation, this study again

demonstrated its predictive role with a hazard ratio for death of 2.307(95% CI 1.073 to 4.962) for patients with unmethylated *MGMT* promoter status (P=0·03). This phase II study introduces the question – should more elderly patients with poor performance status be primarily treated with TMZ monotherapy? Or should TMZ monotherapy be employed only in those whose tumor harbors a methylated *MGMT* promoter?

Although *MGMT* promoter methylation status is increasingly available it still not used in all centres. In the future increasing evidence favoring MGMT testing is likely to demand more widespread availability; for example the European Association for Neuro-Oncology (EANO) guideline for the diagnosis and treatment of malignant gliomas has already declared that MGMT promoter methylation status testing is standard of care[30]. There have been some controversies regarding the methodology of *MGMT* testing, with some centers preferring pyrosequencing and others utilizing PCR. Immunohistochemistical assessment of *MGMT* does not appear to correlate with overall survival.[31]

Bevacizumab

Three uncontrolled studies indicate that the vascular endothelial growth factor (VEGF) antibody bevacizumab may have increased activity in elderly patients with glioblastoma.[32-34] In 2014, the efficacy of bevacizumab in newly diagnosed glioblastoma patients has been reported by two large, placebo-controlled, randomized trials.[35,36] The Avastin in Glioblastoma (AVAglio) phase III study evaluated the effect of the addition of bevacizumab to focal radiotherapy with concurrent TMZ, to the adjuvant component and then beyond the adjuvant component until progression.[34] Although improved progression-free survival (HR 0·65 (0·56–0·75)), preservation of baseline quality of life and performance status were reported, there was no improvement in

overall survival. Stratified by age over 70 years, the statistical significance with regards to PFS was lost [HR 0·78 (0·46–1·33)]; however this may reflect an issue of statistical power and small subgroups rather than a lack of clinical efficacy. The RTOG 0825 trial, sharing a similar design, also failed to demonstrate an overall survival benefit[35] but in contrast to the AVAglio study, a greater deterioration clinically assessed by patient reported outcome questionnaire, was evident in the bevacizumab group. There were differences in the design of these two studies that may influence determination of progression and patient reports outcomes. Radiological assessment in the RTOG 0825 study was by serial measurement of cross-sectional diameter and use of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST)[37] committee whereas the AVAglio study utilized an adaptation of the Macdonald criteria, similar to the newer RANO criteria, which takes into account the issues of pseudoprogression, pseudoresponse and changes in the non-enhancing disease.[38] Ongoing discussion and analyses may further clarify the apparent discordant results with regard to progression-free survival in these two pivotal trials.

No clinical or tissue based biomarkers have yet been prospectively shown to be associated with benefit from bevacizumab although patients with glioblastomas harbouring a proneural subtype may derive the most benefit.[39] At present bevacizumab has no role in the standard upfront treatment of glioblastoma; however, future clinical trials may attempt to target specific groups of patients defined by sets of biomarkers. The randomized Avastin plus Radiotherapy in Elderly Patients with Glioblastoma (ARTE) study, a phase II trial, will explore whether the addition of bevacizumab to radiotherapy improves outcome in elderly patients with newly diagnosed glioblastoma without *MGMT* promoter methylation (M. Weller, personal communication).

Symptomatic management

Glioblastoma can cause many difficult symptoms ranging from fatigue to those associated with raised intracranial pressure. Seizures may often occur as well as cognitive, motor or sensory deficits occurring in a location-dependent manner. Corticosteroids are often required to control symptoms of cerebral edema and their utility over time must be balanced with potential side effects such as proximal myopathy, steroid-induced diabetes, and osteoporotic fractures which can be debilitating. Furthermore, corticosteroids may reduce the benefit from TMZ in the most promising MGMT promoter methylated subgroup.[40] Anti-seizure medications are also often warranted. There is no randomised evidence pertaining to palliative care in the glioblastoma setting. However, based on a randomised study in non-small lung cancer, which demonstrated the addition of palliative care not only improved quality of life but also increased overall survival, many would advocate the early incorporation of palliative care support.[41]

Population-based retrospective studies

For glioblastoma, like many other cancers, results from randomized clinical trials (RCTs) may not reflect 'real world" outcomes as described in population based studies. Several large population based studies have shown that many elderly patients do not receive the 'gold standard' treatment. For example, despite the increasing body of evidence regarding the important benefit of resection rather than biopsy, numerous international pattern of care studies[42-46] demonstrate a much higher rate of biopsy alone rather than attempted resection in the elderly population.

The SEER database study published by Scott et. al. reported that among 2836 patients, only 46% of those over the age of 70 received both surgery and radiotherapy, with omission of

treatment associated with poorer survival.[19] A similar SEER study of 4,137 patients with glioblastoma, aged 65 or older, reported a median overall survival of 4 months and described age to be associated with lower odds of resection and provision of RT or chemotherapy.[19] The Princess Margaret Cancer Centre published outcomes of 131 patients aged greater than 70 treated in the 'temozolomide era' between 2004 and 2008.[47] Elderly patients were more likely to receive best supportive care or 'palliative' doses of radiotherapy with only 1 patient receiving 60Gy in 30 fractions in combination with TMZ. Only 6 patients (5%) received TMZ post-radiation, with only a median of 2.5 cycles administered. A retrospective review of 235 patients aged 65 or over treated between 2006 and 2013 at the Odette Cancer Center in Toronto provides a more contemporary overview regarding provision of care in the elderly setting.[48] With a median survival of approximately 2 months, 19% of patients were deemed not suitable for active treatment.

There is a likely another subgroup of elderly patients not reflected in statistics who might be presumptively diagnosed on radiological investigations (e.g. imaging for suspected stroke) but for various reasons (e.g. comorbidities, patient and family preference) do not proceed even to a biopsy. Of course, in certain scenarios, e.g. bedbound patient with dementia, it may be inappropriate to pursue active management.

Survivorship in the 'real world' would appear less favorable to that quoted in RCTs and may be a reflection of both physician preference to not to administer treatment in a group previously not studied as well as patient choice. A patient-centered approach is important, as in all aspects of medicine, and treatment decisions need to involve a patient's own preferences and goals of care should be a focus early in the discussion regarding management.

Practical aspects:

Practical considerations such as performance status and even the ability of the patient to get to appointments can also come into play, as many of these patients are no longer driving. For example, a mobile elderly patient with a poor short-term memory, but with a strong family network advocating for active treatment, is far more likely to be treated than a socially isolated patient. If a cognitively intact patient with poor mobility is keen for treatment; again the presence of supportive family will often make a difference impacting on decision-making.

Often rehabilitation is not offered for glioblastoma patients postoperatively. However, there is evidence that postoperative rehabilitation in this setting is just as useful as in the stroke setting[49,50] and should be considered where possible. There are observational studies which show improvement in patients' functional status during the course of rehabilitation therapy, including the functional independence measure (FIM)[51,52] and referral for rehabilitation is advocated.[53]

Elderly patients and their caregivers may have numerous symptoms or challenges ahead. Challenges include treatment and tumor-related symptoms and deficits, seizures, headaches, communication difficulties (e.g. expressive or receptive aphasia), personality and behaviour changes (e.g. frontal syndrome with disinhibition and emotional lability), poor concentration, poor memory, fatigue, weakness, mobility; hemiparesis, impaired judgement/insight and depression (reactive versus major). These challenges can be even more difficult to manage in the setting of comorbidities and polypharmacy often faced by elderly patients.

The clinical journey is a complex one and can involve interaction with many health professionals- including neurosurgeon, radiation oncologist (and radiation therapists), medical oncologist, palliative care physician, occupational therapist, physiotherapist, neurologist, endocrinologist (for steroid-induced diabetes) or diabetic educator, social worker, pharmacist,

psychologist, speech pathologist etc. and ideally a cancer care coordinator should be available, where possible, to help the patient navigate through this difficult pathway.

Caregiver burnout is also very important for clinicians to be aware of. Recent studies have demonstrated that the global quality of life is often poorer in the caregiver than in the patients themselves.[54,55] Often, in the elderly setting, a spouse (if there is one) has their own co-morbidities to deal with and struggles to manage both physically and emotionally with the complexities involved with caring for a partner with glioblastoma.

Conclusion and recommendations

Selecting the appropriate treatment for an elderly patient with a newly diagnosed glioblastoma is challenging and a patient-centred approach is essential. Randomised evidence to guide treatment decisions is emerging (table 2) and there is less reason for nihilism. Initial consideration should include the appropriateness and extent of surgical intervention. With frailty and potential comorbidities there may be increased perioperative complications and prolonged recovery; however, maximal safe surgical resection should be considered. Subsequent management should incorporate initial symptomatic management including titration of corticosteroids and suitable anti-seizure medication if required. Early introduction of palliative care may have a role in many patients. Management should be based upon the fitness of the patient, performance status, and *MGMT* promoter methylation status (Figure 2).[56] Standard radiotherapy of 60Gy in 30 fractions with concurrent and adjuvant TMZ can be utilized for most patients under the age of 70 and of appropriate fitness. In patients over the age of 70 there is evidence of efficacy for both radiotherapy alone and TMZ monotherapy respectively; the results of the NCIC-CTG/EORTC/TROG clinical trial will assess the benefit of hypofractionated

radiotherapy with concurrent TMZ compared to radiotherapy alone. Most patients over 70 years of age appear not to benefit from conventional radiation schedules such as 60Gy in 30 fractions and a hypofractionated schedule is recommended. *MGMT* may turn out to be even more important in the setting of elderly patients than in younger patients in terms of guiding management decisions. Ideally *MGMT* promoter methylation status should be determined on all patients 65 years and older. Patients lacking *MGMT* promoter methylation should be considered for a course of hypofractionated radiation therapy alone while those with methylated tumors may be offered temozolomide alone. Selection of these treatments requires an interdisciplinary discussion of the risks and benefits of RT versus TMZ, incorporation of the patient's own goals of care, and patient preference.

Some of the current algorithms for elderly glioblastoma patients are based on extrapolations from small and underpowered studies, but hopefully over the next few years, higher levels of evidence from larger maturing phase III studies will ensure future recommendations are more robust.

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Figure Legends

Figure 1: Overall Survival of Glioblastoma Patients Treated in Ontario, Canada Stratified by Decade of Age

Figure 2 Figure 2: Flow diagram of treatment considerations for elderly Glioblastoma patients (a) 65-70 and (b) >70

Table Legends

Table 1: Average age adjusted incidence per 100,000 and relative survival for GB stratified by age (CBTRUS)[2]

Table 2: Randomised clinical evidence for elderly glioblastoma patients.

Glioblastoma in the Elderly: Making Sense of the Evidence

Matthew Mason[1], Normand Laperriere[1], Wolfgang Wick[2], David A. Reardon[3], Annika Malmstrom[4], Elizabeth Hovey[5], Michael Weller[6] & James R Perry[7]

1) Department of Radiation Oncology, Princess Margaret Cancer Centre, University of Toronto, 610 University Avenue, Toronto, ON, M5T 2M9 Canada

2) Neurology Clinic & National Center for Tumor Disease and Neurology Clinic, Heidelberg University Medical Center & DKFZ, Heidelberg, Germany.

3) Center for Neuro-Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, Dana 2134, Boston, MA 02215-5450 USA

4) Department of Advanced Home Care and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

5) Department of Medical Oncology, Prince of Wales Hospital, Barker Street, Randwick NSW 2031 Australia

6) Department of Neurology, University Hospital Zurich, Frauenklinikstrasse 26, CH-8091 Zürich, Switzerland

7) Division of Neurology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, M4N 3M5 Canada

Running Title: Glioblastoma in the Elderly

Corresponding Author:
James Perry MD, FRCPC
Division of Neurology, Sunnybrook Health Sciences and Odette Cancer Centre,
A402, 2075 Bayview Avenue
University of Toronto, Toronto, Ontario, Canada
M4N 3M5
Ph: 416 480 4766
Fax: 416 480 5054
Email: James.Perry@sunnybrook.ca

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Abstract:

Glioblastoma is a highly malignant neoplasm, notorious for its poor prognosis. The median age of diagnosis is 64 years, with an increasing number of patients diagnosed over the age of seventy. Managing elderly patients with this condition is challenging. Management pathways may include surgery, radiotherapy (RT), chemotherapy and best supportive care (BSC). Many clinical trials in oncology exclude elderly patients, including some of those for malignant brain tumors leaving less evidence to guide treatment in the these patients. Recent advances in molecular diagnostics and biomarkers, such as 06-methylguanine-DNA-methyltransferase (*MGMT)* promoter methylation status, may help guide optimal treatment selection. Focusing on available randomized data, this review provides a practical overview of the evidence for the treatment of newly diagnosed glioblastoma in the elderly including management recommendations.

Keywords: Elderly, glioblastoma, surgery, radiotherapy, chemotherapy

Convention is to define the 'elderly' population as exceeding a specified chronological age which varies with temporal, geographical, social and cultural factors. Managing elderly patients can be challenging; medical comorbidities, multiple concomitant medications, and increasing fragility of health alter drug efficacy and the magnitude and spectrum of adverse effects related to treatment. With age, the natural insidious change of physiology and constitution affects pharmacokinetic processes with regards to absorption, metabolism, distribution and drug clearance.[1] Many clinical trials in oncology exclude elderly patients, including some of those for malignant brain tumors; as such there is less evidence to guide treatment in the elderly cohort. This review provides a practical overview of the evidence for the treatment of newly diagnosed glioblastoma in the elderly.

Epidemiology

Glioblastoma is a highly malignant neoplasm, notorious for its poor prognosis. The Central Brain Tumour Registry of the United States (CBTRUS) statistical report, which collates epidemiological data from over 50 state cancer registries, identified 112,458 malignant primary brain and central nervous system (CNS) tumors between 2006 and 2010 of which 45.2% were glioblastomas.[2] A median age of 64 at diagnosis and an average age-adjusted incidence rate per of 3·19 (3·16-3·21) per 100,000 were reported. Stratification by age detected an increase in incidence with age, and the peak rate of 14·93 in the 75-84 age range. Of note is the marked decrease in survival with advancing age (table 1). The 1-year and 2-year relative survival rates of

40·7% and 14·2% for patients aged 55-64 falls to 9·2% and 2·6% for patients aged 75 or older. An Ontario (Canada) population-based cohort study of all patients diagnosed with glioblastoma between 1982 and 1994 found poorer survival with respect to each increasing decade of age (Figure 1 courtesy of Paszat et. al. Unpublished 1999). Whether this poorer survival is a reflection of differing provisions of care based on chronological age or reflects more aggressive tumor biology, or both, is presently unclear.

The histologic hallmarks of glioblastoma, as defined by the World Health Organization (WHO), include cellular polymorphism, nuclear atypia, a high mitotic index, microvascular proliferation and necrosis.[3] With the emergence of personalized medicine, molecular diagnostics are increasingly used to improve the treatment and survival associated with glioblastoma. Prognostic biomarkers such as TP53 mutation, 1p deletion, cyclin dependent kinase (CDK) N2A/p16 deletion and epidermal growth factor receptor (EGFR) amplification vary with age[4]. In a histological review of 140 patients, *TP53* mutations and *EGFR* amplification had differing prognostic significance when stratifying by age, with TP53 mutations being positively prognostic for younger patients and negative for older patients (<70yrs 0.84; 95% CI 0.49 –1.42 versus >70yrs HR 7.54; 95% CI 2.38–23.87)[4]. Conversely *EGFR* amplification in the context of older patients was positively prognostic yet in younger patients it was negatively prognostic.[4]

More recently gene expression-based molecular analysis has been utilized to categorize glioblastoma into subtypes including proneural, neural, classical and mesenchymal subtypes.[5] Lee et al. performed a meta-analysis which substantiated the presence of these subtypes, as identified by genetic signature and suggested that the prognostic effect of age may in fact be a reflection of the differing prevalence of specific subtypes at differing ages; for example the

proneural subtype appears to occur more often in younger patients and is associated with longer survival.[6] Presently these markers do not have a defined role in clinical practice with regards to daily management decisions and remain under investigation. Of note, positive prognostic biomarkers, like mutations of *isocitrate dehydrogenase (IDH)* are virtually absent in glioblastoma of the elderly; similarly the general DNA methylation levels in the tumor tissue seem to be low. Despite this the frequency of *O6-Methylguanine-DNA methyltransferase (MGMT)* promoter methylation, itself an important positive predictive marker, does not vary with age.[7]

Surgery

In younger patients, maximal safe resection is advocated with the intent of preserving neurological function, providing maximal tissue for molecular profiling, and improving overall survival. Analysis of the extent of surgery in Radiation Therapy Oncology Group (RTOG) randomised trials, found significant improvement in survival with partial/total resection versus biopsy alone.[8] Review of an unselected population of 345 newly diagnosed glioblastoma patients from the German Glioma Network (GGN) demonstrated gross tumour resection to be associated with superior overall survival (OS) (median 17·1 months) compared to incomplete resection (median 11·7 months) and biopsy alone (median 8·7 months).[9] A multivariate analysis of 416 glioblastoma patients treated at a single institution between 1993 and 1999 reported resections of tumour volume in the order of 98% or greater to be associated with significant survival advantage (median survival 13 months, 95% CI 11·4–14·6 months versus 8·8 months (95% CI 7·4–10·2 months; $p < 0·0001$).[10]

There is one randomized trial pertaining to surgical intervention, including elderly patients with glioblastoma. This small study of 30 patients assessed the role of debulking surgery compared to biopsy alone.[11] Patients aged 65 or older with KPS >60 were randomized to open craniotomy and resection [14 patients with a median age of 70 (66-80)] or stereotactic biopsy [16 patients with a median of age 72 (67 -79)]. Surgical resection resulted in superior overall survival (171 days (95% CI 146–278) vs. 85 days (95% CI 55–157) p = 0·0346). More recently, a case-control study with a subgroup analysis of 52 patients aged 70 or over found a median survival of 4·5 months and 3 months for surgical resection and needle biopsy respectively (p = 0·03).[12] Perhaps the most relevant trial for the topic is the Neuro-oncology Working Group of the German Cancer Society NOA-08 study which found extent of surgery to be an independent prognostic factor for overall survival among glioblastoma patients 65 years and older.[13] Furthermore, multivariate analysis of all patients (n=342) participating in the Nordic trial of standard vs. hypofractionated radiotherapy vs. chemotherapy alone in newly diagnosed glioblastoma patients 65 years of age or older also demonstrated a survival benefit favoring surgery over biopsy alone (biopsy versus resection HR 1·50 (1·17 -1·92) p =0·001).[14]

Standard post-operative management for newly diagnosed glioblastoma

The European Organisation for Research and Treatment of Cancer (EORTC) 26981-22981/National Cancer Institute of Canada Clinical Trials Group (NCIC) CE.3 randomised phase III trial assessed the addition of temozolomide (TMZ) to radiotherapy (RT) in the concomitant and sequential adjuvant setting in glioblastoma patients aged 18-70.[15] Median age was 56 (range 19-71) and the selected population required Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. The addition of TMZ resulted in a median survival benefit of 2·5

months; 14·6 months (95% CI 13·2- 16·8) compared with 12·1 months (95%CI 11·2 -13·0) for radiotherapy alone. The 5-year analysis of this trial confirmed a persisting advantage and this has become the standard of care post-surgical resection for patients less than 70 years of age and of appropriate performance status.[16] In a recent review Laperriere et. al. noted that subgroup analysis of this trial demonstrated a trend to benefit in the more elderly subgroups, albeit with a less impressive hazard ratio and without reaching statistical significance. Specifically, there was diminishing benefit of combined treatment with increasing age (61-65 years: HR 0.64 p = 0.096 and 66–70 years: HR = 0·78 p = 0·34) compared to the overall group (HR 0·6, 95%CI 0·5-0·7; p<0·0001).[17] This may reflect less robust effects of the combined approach in the elderly or may be due to lower statistical power in the subgroup analysis.

Radiation for elderly patients

Randomized trials have long demonstrated a survival benefit from post-operative radiotherapy in the management of glioblastoma and more recently several trials have focused on the elderly. The French ANOCEF group found a median survival benefit of 12.2 weeks in favour of RT plus best supportive care (BSC) versus BSC alone.[18] Patients aged 70 or older with a KPS >70 and a diagnosis of glioblastoma or anaplastic astrocytoma were randomized postoperatively to receive BSC [(42 patients (median age 73; range 70-85)] or BSC and 50 Gy in 1.8 Gy fractions to a clinical target volume (CTV) consisting of enhancing tumour with a 2cm margin [(39 patients (median age 75; range 70-84)]. Overall survival was 16·9 (95% CI, 13·4 to 21·4) and 29·1 weeks (95% CI, 25·4 to 34·9) respectively. No significant difference was detected with regards to quality of life; however, Health Related Quality of Life (HRQoL) assessments were

incomplete. Cox proportional hazard modelling revealed that extent of surgery was associated with increased survival.

Scott et al. performed a large retrospective review of elderly glioblastoma patients diagnosed between 1993 and 2005.[19] The study sample of 2836 patients identified from the Surveillance, Epidemiology, and End Results (SEER) registry database had a median age of 76·9 years (range 71·0–98·0). Kaplan-Meier analysis revealed median cancer-specific survivals of 8 months for patients undergoing both surgery and postoperative radiotherapy, 4 months for radiation alone, 3 months for surgery alone and 2 months for neither surgery nor radiotherapy (log rank p<0·001). Multivariate analysis suggested radiotherapy significantly increased cancer-specific survival after adjusting for tumour size, tumour location, surgery and patient demographics with a hazard ratio (HR) of 0·43 (95% CI, 0·38–0·49). [19]

The biological effect of radiation on tumour and normal tissues is dependent upon the provision of dose over time as well as intrinsic radio-sensitivity (α) and repair capability (ß). Glioblastoma has an alpha-beta ratio (α/ ß) = 8Gy (5·0–10·8)[20] which is in the range of most tumours, while the alpha-beta ratio is approximately 2 for the normal central nervous system. As a result of this difference, hypofractionation reduces overall treatment time and may minimize the potential for tumor cell repopulation and provides a practical convenience for an elderly frail population. Roa et. al. randomized patients aged 60 or older to radiotherapy given as 60Gy in 30 fractions (47 patients, mean age 72.4 yrs, SD 5·4) or a hypofractionated regimen of 40Gy in 15 fractions (48 patients, mean 71·0 yrs, SD 5·5).[21] While this study was not sufficiently powered to conclude equivalence of these two fractionation schedules it suggested no significant differences in OS [median 5.1 months for the standard RT arm versus 5·6 months for the shorter course (log rank p = 0·57)], survival at 6 months (44·7% standard RT versus 41·7% hypofractionated RT),

or HRQoL. More patients required an increase of corticosteroid dose following the standard radiotherapy schedule compared to the hypofractionated course (p= 0·02).

The Nordic trial incorporated a different hypofractionated radiotherapy schedule.[14] There were 3 treatment arms including standard radiotherapy of 60Gy in 30 fractions, hypofractionated radiotherapy of 34Gy in 10 fractions or temozolomide 200mg/m2 days 1-5 every 28 days for up to 6 cycles. Standard radiotherapy (60Gy/30) was not routinely offered to elderly patients in some study sites so randomization between just the hypofractionated radiotherapy and temozolomide arms was permitted. Two hundred and ninety one glioblastoma patients (initially aged 60 years or older then in view of EORTC 26981-22981/NCIC-CTG CE.3 the age eligibility was adjusted so that patients 60-65 years old fit for combined treatment were excluded) were randomized to standard radiotherapy (n=100), hypofractionated radiotherapy (n=98) or temozolomide alone (n=93). A further 51 patients were randomized to either hypofractionated radiotherapy (n=25) or TMZ (n=26) by those centers that did not offer 60Gy in 30 fractions as their standard care.

The median age was 70 for both the hypofractionated and the standard radiotherapy groups. Median survival in the hypofractionated group was increased by 1·5 months compared to standard radiation in the three-arm comparison. Interestingly, on stratification by age, the advantage of hypofractionated radiation appeared better in patients over the age of 70 (7·0 (5·2–8·8) versus 5·2 (4·0–6·3) months). Treatment completion according to protocol was more frequent with the hypofractionated schedule (95% versus 72%). Salvage treatment was received for a similar proportion of patients in both groups while reported toxicity was not different between groups.

Temozolomide and O-6-methylguanine-DNA methyltransferase

The alkylating agent TMZ has activity in glioblastoma, and in combination with radiotherapy followed sequentially by a 6 month maintenance course represents the current standard of care for many patients. The mechanism of anti-tumour activity is believed to arise through methylation of DNA at the O-6 position of guanine by monomethyl-triazeno-imidazole-carboxyamide (MTIC), a non-enzymatic chemical degradation product of temozolomide.[22]

MGMT is a DNA repair protein implicated in resistance to alkylating agents.[23] Methylation of the *MGMT* promoter, located at 10q26, leads to suppression of *MGMT* gene expression and an increased likelihood of clinical benefit.[23-25] Hegi et al. assessed the *MGMT* promoter methylation status of patients randomized in the EORTC trial 26981/ NCIC CE.3 trial.[25] Regardless of treatment arm, OS was longer in patients with *MGMT* promoter methylation; 18.2 months compared with 12.2 months [HR for death 0·45 (95% CI 0·32 - 0·61)]. The magnitude of this effect was more substantial for patients receiving TMZ compared with those receiving radiation alone (P=0·007 vs. P=0·06, log-rank test). Of note, the majority of patients allocated to radiotherapy alone received alkylating agent chemotherapy as salvage treatment further supporting the use of concomitant therapy 'upfront' in newly diagnosed patients.[25] The prognostic significance of *MGMT* promoter methylation status was prospectively corroborated in the RTOG 0525 randomized study of TMZ dose density in the adjuvant setting. In this study, dose-dense TMZ (n=422) failed to demonstrate a survival advantage over standard dosing (n=411).[26] The absence of a TMZ-free control arm did not allow distinction between prognostic and predictive properties.

For elderly patients not suitable for the combined modality approach, recent evidence supports consideration of TMZ alone particularly for tumors harbouring *MGMT* promoter methylation.[27] Temozolomide alone was assessed in the Nordic study,[14] which found longer survival for both TMZ alone and hypofractionated radiotherapy over standard radiotherapy in patients older than 65 years of age. Comparison of TMZ and hypofractionated radiotherapy revealed no significant difference in overall survival (7·4 versus 8·4 months HR 0·82 95%CI 0·63-1·06). In the head to head comparison of TMZ versus hypofractionated radiation, 36% of the TMZ recipients had subsequent radiation and 29% of the hypofractionated group had salvage chemotherapy. *MGMT* promoter methylation status was available in 258 (75%) of 342 patients. Patients with *MGMT* promoter methylated tumors receiving TMZ survived 2.9 months longer than those with unmethylated tumors (HR 0·56, 95% CI 0·34-0·93, p=0·02). No survival advantage was identified based on *MGMT* promoter methylation status within the cohort receiving radiation (HR 0·97, 95% CI 0·69-1·38, p=0·81). Although the intent for the TMZ group was to complete six cycles, at least two cycles were administered to 86% of patients, and only 34% completed all six cycles. Haematological toxicity as well as nausea and vomiting were more frequent as would be expected in the TMZ cohort. In addition, a treatment-related death involving thrombocytopenia highlights that prescribing chemotherapy is not without the potential for serious toxicity.

In the NOA-08 study,[13] 192 patients received TMZ (1 week on, 1 week off schedule 100 mg/m2 days 1–7) and 178 patients received 60Gy radiotherapy alone over 6–7 weeks to the gross tumour volume (GTV) + 2 centimeters. Median overall survival was similar for the two treatment arms: 8·6 months in the TMZ group and 9·6 months in the radiotherapy group (HR

1·09, 95% CI 0·84–1·42, p non-inferiority=0·033). *MGMT* promoter methylation status was available in 55% of patients receiving TMZ and 57% of patients receiving radiation with a predictive benefit seen for patients receiving the alkylating agent in the context of *MGMT* promoter methylated tumors. Hematological toxicity, abnormal liver function tests, infections and thromboembolic events were more prevalent in the TMZ group.

These trials found that *MGMT* promoter methylation is a predictive biomarker of benefit from TMZ, but not radiotherapy. The randomized international NCIC/EORTC/TROG study, which completed accrual in September 2013 (JP, personal communication), aims to address the potential benefit of combining short course radiotherapy (40Gy in 15 fractions) with concurrent and adjuvant TMZ in patients over 65 years who have had prior surgery/biopsy at diagnosis and are not deemed suitable for the standard radiotherapy regimen of 60Gy.[28] MGMT status will be assessed in this study.

A phase 2 ANOCEF study suggests that older age and poor KPS should not preclude the use of TMZ alone.[29] This was a non-randomized study which recruited 70 patients with a median age of 77 (range 70-87) and a median KPS of 60 (range 30-60). Intriguingly this study found an improvement of KPS in excess of 10 for 23 (33%) of treated patients with 18 (26%) having a rise to 70 or more. A maximum of 12 cycles of TMZ was planned however the median number of cycles received was only 2 with 20% and 24% of patients having dose delays and dose reductions for hematological toxicity respectively. Grade 3 or 4 hematological toxicities were not insignificant with 13% experiencing grade 3-4 neutropenia and 14% grade 3-4 thrombocytopenia. No deaths were attributed to treatment. Although only 44% of patients were able to have tumor material assessed for *MGMT* promoter methylation, this study again

demonstrated its predictive role with a hazard ratio for death of 2.307(95% CI 1.073 to 4.962) for patients with unmethylated *MGMT* promoter status (P=0·03). This phase II study introduces the question – should more elderly patients with poor performance status be primarily treated with TMZ monotherapy? Or should TMZ monotherapy be employed only in those whose tumor harbors a methylated *MGMT* promoter?

Although *MGMT* promoter methylation status is increasingly available it still not used in all centres. In the future increasing evidence favoring MGMT testing is likely to demand more widespread availability; for example the European Association for Neuro-Oncology (EANO) guideline for the diagnosis and treatment of malignant gliomas has already declared that MGMT promoter methylation status testing is standard of care[30]. There have been some controversies regarding the methodology of *MGMT* testing, with some centers preferring pyrosequencing and others utilizing PCR. Immunohistochemistical assessment of *MGMT* does not appear to correlate with overall survival.[31]

Bevacizumab

Three uncontrolled studies indicate that the vascular endothelial growth factor (VEGF) antibody bevacizumab may have increased activity in elderly patients with glioblastoma.[32-34] In 2014, the efficacy of bevacizumab in newly diagnosed glioblastoma patients has been reported by two large, placebo-controlled, randomized trials.[35,36] The Avastin in Glioblastoma (AVAglio) phase III study evaluated the effect of the addition of bevacizumab to focal radiotherapy with concurrent TMZ, to the adjuvant component and then beyond the adjuvant component until progression.[34] Although improved progression-free survival (HR 0·65 (0·56–0·75)), preservation of baseline quality of life and performance status were reported, there was no improvement in

overall survival. Stratified by age over 70 years, the statistical significance with regards to PFS was lost [HR 0·78 (0·46–1·33)]; however this may reflect an issue of statistical power and small subgroups rather than a lack of clinical efficacy. The RTOG 0825 trial, sharing a similar design, also failed to demonstrate an overall survival benefit[35] but in contrast to the AVAglio study, a greater deterioration clinically assessed by patient reported outcome questionnaire, was evident in the bevacizumab group. There were differences in the design of these two studies that may influence determination of progression and patient reports outcomes. Radiological assessment in the RTOG 0825 study was by serial measurement of cross-sectional diameter and use of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST)[37] committee whereas the AVAglio study utilized an adaptation of the Macdonald criteria, similar to the newer RANO criteria, which takes into account the issues of pseudoprogression, pseudoresponse and changes in the non-enhancing disease.[38] Ongoing discussion and analyses may further clarify the apparent discordant results with regard to progression-free survival in these two pivotal trials.

No clinical or tissue based biomarkers have yet been prospectively shown to be associated with benefit from bevacizumab although patients with glioblastomas harbouring a proneural subtype may derive the most benefit.[39] At present bevacizumab has no role in the standard upfront treatment of glioblastoma; however, future clinical trials may attempt to target specific groups of patients defined by sets of biomarkers. The randomized Avastin plus Radiotherapy in Elderly Patients with Glioblastoma (ARTE) study, a phase II trial, will explore whether the addition of bevacizumab to radiotherapy improves outcome in elderly patients with newly diagnosed glioblastoma without *MGMT* promoter methylation (M. Weller, personal communication).

Symptomatic management

Glioblastoma can cause many difficult symptoms ranging from fatigue to those associated with raised intracranial pressure. Seizures may often occur as well as cognitive, motor or sensory deficits occurring in a location-dependent manner. Corticosteroids are often required to control symptoms of cerebral edema and their utility over time must be balanced with potential side effects such as proximal myopathy, steroid-induced diabetes, and osteoporotic fractures which can be debilitating. Furthermore, corticosteroids may reduce the benefit from TMZ in the most promising MGMT promoter methylated subgroup.[40] Anti-seizure medications are also often warranted. There is no randomised evidence pertaining to palliative care in the glioblastoma setting. However, based on a randomised study in non-small lung cancer, which demonstrated the addition of palliative care not only improved quality of life but also increased overall survival, many would advocate the early incorporation of palliative care support.[41]

Population-based retrospective studies

For glioblastoma, like many other cancers, results from randomized clinical trials (RCTs) may not reflect 'real world" outcomes as described in population based studies. Several large population based studies have shown that many elderly patients do not receive the 'gold standard' treatment. For example, despite the increasing body of evidence regarding the important benefit of resection rather than biopsy, numerous international pattern of care studies[42-46] demonstrate a much higher rate of biopsy alone rather than attempted resection in the elderly population.

The SEER database study published by Scott et. al. reported that among 2836 patients, only 46% of those over the age of 70 received both surgery and radiotherapy, with omission of

treatment associated with poorer survival.[19] A similar SEER study of 4,137 patients with glioblastoma, aged 65 or older, reported a median overall survival of 4 months and described age to be associated with lower odds of resection and provision of RT or chemotherapy.[19] The Princess Margaret Cancer Centre published outcomes of 131 patients aged greater than 70 treated in the 'temozolomide era' between 2004 and 2008.[47] Elderly patients were more likely to receive best supportive care or 'palliative' doses of radiotherapy with only 1 patient receiving 60Gy in 30 fractions in combination with TMZ. Only 6 patients (5%) received TMZ post-radiation, with only a median of 2.5 cycles administered. A retrospective review of 235 patients aged 65 or over treated between 2006 and 2013 at the Odette Cancer Center in Toronto provides a more contemporary overview regarding provision of care in the elderly setting.[48] With a median survival of approximately 2 months, 19% of patients were deemed not suitable for active treatment.

There is a likely another subgroup of elderly patients not reflected in statistics who might be presumptively diagnosed on radiological investigations (e.g. imaging for suspected stroke) but for various reasons (e.g. comorbidities, patient and family preference) do not proceed even to a biopsy. Of course, in certain scenarios, e.g. bedbound patient with dementia, it may be inappropriate to pursue active management.

Survivorship in the 'real world' would appear less favorable to that quoted in RCTs and may be a reflection of both physician preference to not to administer treatment in a group previously not studied as well as patient choice. The definition of 'elderly' varies across clinical trials and may appear to limit the ability to cross-compare data from these studies. That said, the NOA-08 trial had a median age of 72 (66-84) years in the TMZ arm and 72 (66-82) years in the RT arm. Age as a continuous variable or dichotomized at age 70 was not an independent

prognostic factor for either OS or event-free survival[13]; thus the association with age may not be as important in patients older than 70 years. Patients from population-based studies are clearly different that those included in the randomized trials. A patient-centered approach is important, as in all aspects of medicine, and treatment decisions need to involve a patient's own preferences and goals of care should be a focus early in the discussion regarding management.

Practical aspects:

Practical considerations such as performance status and even the ability of the patient to get to appointments can also come into play, as many of these patients are no longer driving. For example, a mobile elderly patient with a poor short-term memory, but with a strong family network advocating for active treatment, is far more likely to be treated than a socially isolated patient. If a cognitively intact patient with poor mobility is keen for treatment; again the presence of supportive family will often make a difference impacting on decision-making.

Often rehabilitation is not offered for glioblastoma patients postoperatively. However, there is evidence that postoperative rehabilitation in this setting is just as useful as in the stroke setting[49,50] and should be considered where possible. There are observational studies which show improvement in patients' functional status during the course of rehabilitation therapy, including the functional independence measure (FIM)[51,52] and referral for rehabilitation is advocated.[53]

Elderly patients and their caregivers may have numerous symptoms or challenges ahead. Challenges include treatment and tumor-related symptoms and deficits, seizures, headaches, communication difficulties (e.g. expressive or receptive aphasia), personality and behaviour changes (e.g. frontal syndrome with disinhibition and emotional lability), poor concentration, poor memory, fatigue, weakness, mobility; hemiparesis, impaired judgement/insight and

depression (reactive versus major). These challenges can be even more difficult to manage in the setting of comorbidities and polypharmacy often faced by elderly patients.

The clinical journey is a complex one and can involve interaction with many health professionals- including neurosurgeon, radiation oncologist (and radiation therapists), medical oncologist, palliative care physician, occupational therapist, physiotherapist, neurologist, endocrinologist (for steroid-induced diabetes) or diabetic educator, social worker, pharmacist, psychologist, speech pathologist etc. and ideally a cancer care coordinator should be available, where possible, to help the patient navigate through this difficult pathway.

Caregiver burnout is also very important for clinicians to be aware of. Recent studies have demonstrated that the global quality of life is often poorer in the caregiver than in the patients themselves.[54,55] Often, in the elderly setting, a spouse (if there is one) has their own co-morbidities to deal with and struggles to manage both physically and emotionally with the complexities involved with caring for a partner with glioblastoma.

Conclusion and recommendations

Selecting the appropriate treatment for an elderly patient with a newly diagnosed glioblastoma is challenging and a patient-centred approach is essential. Randomised evidence to guide treatment decisions is emerging (table 2) and there is less reason for nihilism. Initial consideration should include the appropriateness and extent of surgical intervention. With frailty and potential comorbidities there may be increased perioperative complications and prolonged recovery; however, maximal safe surgical resection should be considered. Subsequent management should incorporate initial symptomatic management including titration of corticosteroids and suitable anti-seizure medication if required. Early introduction of palliative

care may have a role in many patients. Management should be based upon the fitness of the patient, performance status, and *MGMT* promoter methylation status (Figure 2).[56] Standard radiotherapy of 60Gy in 30 fractions with concurrent and adjuvant TMZ can be utilized for most patients under the age of 70 and of appropriate fitness. In patients over the age of 70 there is evidence of efficacy for both radiotherapy alone and TMZ monotherapy respectively; the results of the NCIC-CTG/EORTC/TROG clinical trial will assess the benefit of hypofractionated radiotherapy with concurrent TMZ compared to radiotherapy alone. Most patients over 70 years of age appear not to benefit from conventional radiation schedules such as 60Gy in 30 fractions and a hypofractionated schedule is recommended. *MGMT* may turn out to be even more important in the setting of elderly patients than in younger patients in terms of guiding management decisions. Ideally *MGMT* promoter methylation status should be determined on all patients 65 years and older. Patients lacking *MGMT* promoter methylation should be considered for a course of hypofractionated radiation therapy alone while those with methylated tumors may be offered temozolomide alone. Selection of these treatments requires an interdisciplinary discussion of the risks and benefits of RT versus TMZ, incorporation of the patient's own goals of care, and patient preference.

Some of the current algorithms for elderly glioblastoma patients are based on extrapolations from small and underpowered studies, but hopefully over the next few years, higher levels of evidence from larger maturing phase III studies will ensure future recommendations are more robust.

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Figure Legends

Figure 1: Overall Survival of Glioblastoma Patients Treated in Ontario, Canada Stratified by Decade of Age

Figure 2 Figure 2: Flow diagram of treatment considerations for elderly Glioblastoma patients (a) 65-70 and (b) >70

Table Legends

Table 1: Average age adjusted incidence per 100,000 and relative survival for GB stratified by age (CBTRUS)[2]

Table 2: Randomised clinical evidence for elderly glioblastoma patients.

Glioblastoma in the Elderly: Making Sense of the Evidence

Matthew Mason[1], Normand Laperriere[1], Wolfgang Wick[2], David A. Reardon[3], Annika Malmstrom[4], Elizabeth Hovey[5], Michael Weller[6] & James R Perry[7]

1) Department of Radiation Oncology, Princess Margaret Cancer Centre, University of Toronto, 610 University Avenue, Toronto, ON, M5T 2M9 Canada

2) Neurology Clinic & National Center for Tumor Disease and Neurology Clinic, Heidelberg University Medical Center & DKFZ, Heidelberg, Germany.

3) Center for Neuro-Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, Dana 2134, Boston, MA 02215-5450 USA

4) Department of Advanced Home Care and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

5) Department of Medical Oncology, Prince of Wales Hospital, Barker Street, Randwick NSW 2031 Australia

6) Department of Neurology, University Hospital Zurich, Frauenklinikstrasse 26, CH-8091 Zürich, Switzerland

7) Division of Neurology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, M4N 3M5 Canada

Running Title: Glioblastoma in the Elderly

Corresponding Author:
James Perry MD, FRCPC
Division of Neurology, Sunnybrook Health Sciences and Odette Cancer Centre,
A402, 2075 Bayview Avenue
University of Toronto, Toronto, Ontario, Canada
M4N 3M5
Ph: 416 480 4766
Fax: 416 480 5054
Email: James.Perry@sunnybrook.ca

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DAR: Speakers' Bureau (compensated): Merck and Roche/Genentech; Advisory Board member (compensated): Roche/Genentech; Cavion; Novartis; Midatech; Stemline Therapeutics; Momenta Pharmaceuticals; Research Support: Celldex Therapeutics; Incyte

AM: none declared

EH: Glioma Advisory Board for Roche Australia, MSD Australia

MW: has received research grants from Acceleron, Actelion, Alpinia Institute, Bayer, Isarna, MSD, Merck & Co, PIQUR and Roche and honoraria for lectures or advisory board participation or consulting from Celldex, Immunocellular, Isarna, Magforce, MSD, Merck & Co, Northwest Biotherapeutics, Pfizer, Roche and Teva.

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Abstract:

Glioblastoma is a highly malignant neoplasm, notorious for its poor prognosis. The median age of diagnosis is 64 years, with an increasing number of patients diagnosed over the age of seventy. Managing elderly patients with this condition is challenging. Management pathways may include surgery, radiotherapy (RT), chemotherapy and best supportive care (BSC). Many clinical trials in oncology exclude elderly patients, including some of those for malignant brain tumors leaving less evidence to guide treatment in the these patients. Recent advances in molecular diagnostics and biomarkers, such as 06-methylguanine-DNA-methyltransferase (*MGMT)* promoter methylation status, may help guide optimal treatment selection. Focusing on available randomized data, this review provides a practical overview of the evidence for the treatment of newly diagnosed glioblastoma in the elderly including management recommendations.

Keywords: Elderly, glioblastoma, surgery, radiotherapy, chemotherapy

Convention is to define the 'elderly' population as exceeding a specified chronological age which varies with temporal, geographical, social and cultural factors. Managing elderly patients can be challenging; medical comorbidities, multiple concomitant medications, and increasing fragility of health alter drug efficacy and the magnitude and spectrum of adverse effects related to treatment. With age, the natural insidious change of physiology and constitution affects pharmacokinetic processes with regards to absorption, metabolism, distribution and drug clearance.[1] Many clinical trials in oncology exclude elderly patients, including some of those for malignant brain tumors; as such there is less evidence to guide treatment in the elderly cohort. This review provides a practical overview of the evidence for the treatment of newly diagnosed glioblastoma in the elderly.

Epidemiology

Glioblastoma is a highly malignant neoplasm, notorious for its poor prognosis. The Central Brain Tumour Registry of the United States (CBTRUS) statistical report, which collates epidemiological data from over 50 state cancer registries, identified 112,458 malignant primary brain and central nervous system (CNS) tumors between 2006 and 2010 of which 45.2% were glioblastomas.[2] A median age of 64 at diagnosis and an average age-adjusted incidence rate per of 3·19 (3·16-3·21) per 100,000 were reported. Stratification by age detected an increase in incidence with age, and the peak rate of 14·93 in the 75-84 age range. Of note is the marked decrease in survival with advancing age (table 1). The 1-year and 2-year relative survival rates of

40·7% and 14·2% for patients aged 55-64 falls to 9·2% and 2·6% for patients aged 75 or older. An Ontario (Canada) population-based cohort study of all patients diagnosed with glioblastoma between 1982 and 1994 found poorer survival with respect to each increasing decade of age (Figure 1 courtesy of Paszat et. al. Unpublished 1999). Whether this poorer survival is a reflection of differing provisions of care based on chronological age or reflects more aggressive tumor biology, or both, is presently unclear.

The histologic hallmarks of glioblastoma, as defined by the World Health Organization (WHO), include cellular polymorphism, nuclear atypia, a high mitotic index, microvascular proliferation and necrosis.[3] With the emergence of personalized medicine, molecular diagnostics are increasingly used to improve the treatment and survival associated with glioblastoma. Prognostic biomarkers such as TP53 mutation, 1p deletion, cyclin dependent kinase (CDK) N2A/p16 deletion and epidermal growth factor receptor (EGFR) amplification vary with age[4]. In a histological review of 140 patients, *TP53* mutations and *EGFR* amplification had differing prognostic significance when stratifying by age, with TP53 mutations being positively prognostic for younger patients and negative for older patients (<70yrs 0.84; 95% CI 0.49 –1.42 versus >70yrs HR 7.54; 95% CI 2.38–23.87)[4]. Conversely *EGFR* amplification in the context of older patients was positively prognostic yet in younger patients it was negatively prognostic.[4]

More recently gene expression-based molecular analysis has been utilized to categorize glioblastoma into subtypes including proneural, neural, classical and mesenchymal subtypes.[5] Lee et al. performed a meta-analysis which substantiated the presence of these subtypes, as identified by genetic signature and suggested that the prognostic effect of age may in fact be a reflection of the differing prevalence of specific subtypes at differing ages; for example the

proneural subtype appears to occur more often in younger patients and is associated with longer survival.[6] Presently these markers do not have a defined role in clinical practice with regards to daily management decisions and remain under investigation. Of note, positive prognostic biomarkers, like mutations of *isocitrate dehydrogenase (IDH)* are virtually absent in glioblastoma of the elderly; similarly the general DNA methylation levels in the tumor tissue seem to be low. Despite this the frequency of *O6-Methylguanine-DNA methyltransferase (MGMT)* promoter methylation, itself an important positive predictive marker, does not vary with age.[7]

Surgery

In younger patients, maximal safe resection is advocated with the intent of preserving neurological function, providing maximal tissue for molecular profiling, and improving overall survival. Analysis of the extent of surgery in Radiation Therapy Oncology Group (RTOG) randomised trials, found significant improvement in survival with partial/total resection versus biopsy alone.[8] Review of an unselected population of 345 newly diagnosed glioblastoma patients from the German Glioma Network (GGN) demonstrated gross tumour resection to be associated with superior overall survival (OS) (median 17·1 months) compared to incomplete resection (median 11·7 months) and biopsy alone (median 8·7 months).[9] A multivariate analysis of 416 glioblastoma patients treated at a single institution between 1993 and 1999 reported resections of tumour volume in the order of 98% or greater to be associated with significant survival advantage (median survival 13 months, 95% CI 11·4–14·6 months versus 8·8 months (95% CI 7·4–10·2 months; $p < 0·0001$).[10]

There is one randomized trial pertaining to surgical intervention, including elderly patients with glioblastoma. This small study of 30 patients assessed the role of debulking surgery compared to biopsy alone.[11] Patients aged 65 or older with KPS >60 were randomized to open craniotomy and resection [14 patients with a median age of 70 (66-80)] or stereotactic biopsy [16 patients with a median of age 72 (67 -79)]. Surgical resection resulted in superior overall survival (171 days (95% CI 146–278) vs. 85 days (95% CI 55–157) p = 0·0346). More recently, a case-control study with a subgroup analysis of 52 patients aged 70 or over found a median survival of 4·5 months and 3 months for surgical resection and needle biopsy respectively (p = 0·03).[12] Perhaps the most relevant trial for the topic is the Neuro-oncology Working Group of the German Cancer Society NOA-08 study which found extent of surgery to be an independent prognostic factor for overall survival among glioblastoma patients 65 years and older.[13] Furthermore, multivariate analysis of all patients (n=342) participating in the Nordic trial of standard vs. hypofractionated radiotherapy vs. chemotherapy alone in newly diagnosed glioblastoma patients 65 years of age or older also demonstrated a survival benefit favoring surgery over biopsy alone (biopsy versus resection HR 1·50 (1·17 -1·92) p =0·001).[14]

Standard post-operative management for newly diagnosed glioblastoma

The European Organisation for Research and Treatment of Cancer (EORTC) 26981-22981/National Cancer Institute of Canada Clinical Trials Group (NCIC) CE.3 randomised phase III trial assessed the addition of temozolomide (TMZ) to radiotherapy (RT) in the concomitant and sequential adjuvant setting in glioblastoma patients aged 18-70.[15] Median age was 56 (range 19-71) and the selected population required Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. The addition of TMZ resulted in a median survival benefit of 2·5

months; 14·6 months (95% CI 13·2- 16·8) compared with 12·1 months (95%CI 11·2 -13·0) for radiotherapy alone. The 5-year analysis of this trial confirmed a persisting advantage and this has become the standard of care post-surgical resection for patients less than 70 years of age and of appropriate performance status.[16] In a recent review Laperriere et. al. noted that subgroup analysis of this trial demonstrated a trend to benefit in the more elderly subgroups, albeit with a less impressive hazard ratio and without reaching statistical significance. Specifically, there was diminishing benefit of combined treatment with increasing age (61-65 years: HR 0.64 p = 0.096 and 66–70 years: HR = 0·78 p = 0·34) compared to the overall group (HR 0·6, 95%CI 0·5-0·7; p<0·0001).[17] This may reflect less robust effects of the combined approach in the elderly or may be due to lower statistical power in the subgroup analysis.

Radiation for elderly patients

Randomized trials have long demonstrated a survival benefit from post-operative radiotherapy in the management of glioblastoma and more recently several trials have focused on the elderly. The French ANOCEF group found a median survival benefit of 12.2 weeks in favour of RT plus best supportive care (BSC) versus BSC alone.[18] Patients aged 70 or older with a KPS >70 and a diagnosis of glioblastoma or anaplastic astrocytoma were randomized postoperatively to receive BSC [(42 patients (median age 73; range 70-85)] or BSC and 50 Gy in 1.8 Gy fractions to a clinical target volume (CTV) consisting of enhancing tumour with a 2cm margin [(39 patients (median age 75; range 70-84)]. Overall survival was 16·9 (95% CI, 13·4 to 21·4) and 29·1 weeks (95% CI, 25·4 to 34·9) respectively. No significant difference was detected with regards to quality of life; however, Health Related Quality of Life (HRQoL) assessments were

incomplete. Cox proportional hazard modelling revealed that extent of surgery was associated with increased survival.

Scott et al. performed a large retrospective review of elderly glioblastoma patients diagnosed between 1993 and 2005.[19] The study sample of 2836 patients identified from the Surveillance, Epidemiology, and End Results (SEER) registry database had a median age of 76·9 years (range 71·0–98·0). Kaplan-Meier analysis revealed median cancer-specific survivals of 8 months for patients undergoing both surgery and postoperative radiotherapy, 4 months for radiation alone, 3 months for surgery alone and 2 months for neither surgery nor radiotherapy (log rank p<0·001). Multivariate analysis suggested radiotherapy significantly increased cancer-specific survival after adjusting for tumour size, tumour location, surgery and patient demographics with a hazard ratio (HR) of 0·43 (95% CI, 0·38–0·49). [19]

The biological effect of radiation on tumour and normal tissues is dependent upon the provision of dose over time as well as intrinsic radio-sensitivity (α) and repair capability (ß). Glioblastoma has an alpha-beta ratio (α/ ß) = 8Gy (5·0–10·8)[20] which is in the range of most tumours, while the alpha-beta ratio is approximately 2 for the normal central nervous system. As a result of this difference, hypofractionation reduces overall treatment time and may minimize the potential for tumor cell repopulation and provides a practical convenience for an elderly frail population. Roa et. al. randomized patients aged 60 or older to radiotherapy given as 60Gy in 30 fractions (47 patients, mean age 72.4 yrs, SD 5·4) or a hypofractionated regimen of 40Gy in 15 fractions (48 patients, mean 71·0 yrs, SD 5·5).[21] While this study was not sufficiently powered to conclude equivalence of these two fractionation schedules it suggested no significant differences in OS [median 5.1 months for the standard RT arm versus 5·6 months for the shorter course (log rank p = 0·57)], survival at 6 months (44·7% standard RT versus 41·7% hypofractionated RT),

or HRQoL. More patients required an increase of corticosteroid dose following the standard radiotherapy schedule compared to the hypofractionated course (p= 0·02).

The Nordic trial incorporated a different hypofractionated radiotherapy schedule.[14] There were 3 treatment arms including standard radiotherapy of 60Gy in 30 fractions, hypofractionated radiotherapy of 34Gy in 10 fractions or temozolomide 200mg/m2 days 1-5 every 28 days for up to 6 cycles. Standard radiotherapy (60Gy/30) was not routinely offered to elderly patients in some study sites so randomization between just the hypofractionated radiotherapy and temozolomide arms was permitted. Two hundred and ninety one glioblastoma patients (initially aged 60 years or older then in view of EORTC 26981-22981/NCIC-CTG CE.3 the age eligibility was adjusted so that patients 60-65 years old fit for combined treatment were excluded) were randomized to standard radiotherapy (n=100), hypofractionated radiotherapy (n=98) or temozolomide alone (n=93). A further 51 patients were randomized to either hypofractionated radiotherapy (n=25) or TMZ (n=26) by those centers that did not offer 60Gy in 30 fractions as their standard care.

The median age was 70 for both the hypofractionated and the standard radiotherapy groups. Median survival in the hypofractionated group was increased by 1·5 months compared to standard radiation in the three-arm comparison. Interestingly, on stratification by age, the advantage of hypofractionated radiation appeared better in patients over the age of 70 (7·0 (5·2–8·8) versus 5·2 (4·0–6·3) months). Treatment completion according to protocol was more frequent with the hypofractionated schedule (95% versus 72%). Salvage treatment was received for a similar proportion of patients in both groups while reported toxicity was not different between groups.

Temozolomide and O-6-methylguanine-DNA methyltransferase

The alkylating agent TMZ has activity in glioblastoma, and in combination with radiotherapy followed sequentially by a 6 month maintenance course represents the current standard of care for many patients. The mechanism of anti-tumour activity is believed to arise through methylation of DNA at the O-6 position of guanine by monomethyl-triazeno-imidazole-carboxyamide (MTIC), a non-enzymatic chemical degradation product of temozolomide.[22]

MGMT is a DNA repair protein implicated in resistance to alkylating agents.[23] Methylation of the *MGMT* promoter, located at 10q26, leads to suppression of *MGMT* gene expression and an increased likelihood of clinical benefit.[23-25] Hegi et al. assessed the *MGMT* promoter methylation status of patients randomized in the EORTC trial 26981/ NCIC CE.3 trial.[25] Regardless of treatment arm, OS was longer in patients with *MGMT* promoter methylation; 18.2 months compared with 12.2 months [HR for death 0·45 (95% CI 0·32 - 0·61)]. The magnitude of this effect was more substantial for patients receiving TMZ compared with those receiving radiation alone (P=0·007 vs. P=0·06, log-rank test). Of note, the majority of patients allocated to radiotherapy alone received alkylating agent chemotherapy as salvage treatment further supporting the use of concomitant therapy 'upfront' in newly diagnosed patients.[25] The prognostic significance of *MGMT* promoter methylation status was prospectively corroborated in the RTOG 0525 randomized study of TMZ dose density in the adjuvant setting. In this study, dose-dense TMZ (n=422) failed to demonstrate a survival advantage over standard dosing (n=411).[26] The absence of a TMZ-free control arm did not allow distinction between prognostic and predictive properties.

For elderly patients not suitable for the combined modality approach, recent evidence supports consideration of TMZ alone particularly for tumors harbouring *MGMT* promoter methylation.[27] Temozolomide alone was assessed in the Nordic study,[14] which found longer survival for both TMZ alone and hypofractionated radiotherapy over standard radiotherapy in patients older than 65 years of age. Comparison of TMZ and hypofractionated radiotherapy revealed no significant difference in overall survival (7·4 versus 8·4 months HR 0·82 95%CI 0·63-1·06). In the head to head comparison of TMZ versus hypofractionated radiation, 36% of the TMZ recipients had subsequent radiation and 29% of the hypofractionated group had salvage chemotherapy. *MGMT* promoter methylation status was available in 258 (75%) of 342 patients. Patients with *MGMT* promoter methylated tumors receiving TMZ survived 2.9 months longer than those with unmethylated tumors (HR 0·56, 95% CI 0·34-0·93, p=0·02). No survival advantage was identified based on *MGMT* promoter methylation status within the cohort receiving radiation (HR 0·97, 95% CI 0·69-1·38, p=0·81). Although the intent for the TMZ group was to complete six cycles, at least two cycles were administered to 86% of patients, and only 34% completed all six cycles. Haematological toxicity as well as nausea and vomiting were more frequent as would be expected in the TMZ cohort. In addition, a treatment-related death involving thrombocytopenia highlights that prescribing chemotherapy is not without the potential for serious toxicity.

In the NOA-08 study,[13] 192 patients received TMZ (1 week on, 1 week off schedule 100 mg/m2 days 1–7) and 178 patients received 60Gy radiotherapy alone over 6–7 weeks to the gross tumour volume (GTV) + 2 centimeters. Median overall survival was similar for the two treatment arms: 8·6 months in the TMZ group and 9·6 months in the radiotherapy group (HR

1·09, 95% CI 0·84–1·42, p non-inferiority=0·033). *MGMT* promoter methylation status was available in 55% of patients receiving TMZ and 57% of patients receiving radiation with a predictive benefit seen for patients receiving the alkylating agent in the context of *MGMT* promoter methylated tumors. Hematological toxicity, abnormal liver function tests, infections and thromboembolic events were more prevalent in the TMZ group.

These trials found that *MGMT* promoter methylation is a predictive biomarker of benefit from TMZ, but not radiotherapy. The randomized international NCIC/EORTC/TROG study, which completed accrual in September 2013 (JP, personal communication), aims to address the potential benefit of combining short course radiotherapy (40Gy in 15 fractions) with concurrent and adjuvant TMZ in patients over 65 years who have had prior surgery/biopsy at diagnosis and are not deemed suitable for the standard radiotherapy regimen of 60Gy.[28] MGMT status will be assessed in this study.

A phase 2 ANOCEF study suggests that older age and poor KPS should not preclude the use of TMZ alone.[29] This was a non-randomized study which recruited 70 patients with a median age of 77 (range 70-87) and a median KPS of 60 (range 30-60). Intriguingly this study found an improvement of KPS in excess of 10 for 23 (33%) of treated patients with 18 (26%) having a rise to 70 or more. A maximum of 12 cycles of TMZ was planned however the median number of cycles received was only 2 with 20% and 24% of patients having dose delays and dose reductions for hematological toxicity respectively. Grade 3 or 4 hematological toxicities were not insignificant with 13% experiencing grade 3-4 neutropenia and 14% grade 3-4 thrombocytopenia. No deaths were attributed to treatment. Although only 44% of patients were able to have tumor material assessed for *MGMT* promoter methylation, this study again

demonstrated its predictive role with a hazard ratio for death of 2.307(95% CI 1.073 to 4.962) for patients with unmethylated *MGMT* promoter status (P=0·03). This phase II study introduces the question – should more elderly patients with poor performance status be primarily treated with TMZ monotherapy? Or should TMZ monotherapy be employed only in those whose tumor harbors a methylated *MGMT* promoter?

Although *MGMT* promoter methylation status is increasingly available it still not used in all centres. In the future increasing evidence favoring MGMT testing is likely to demand more widespread availability; for example the European Association for Neuro-Oncology (EANO) guideline for the diagnosis and treatment of malignant gliomas has already declared that MGMT promoter methylation status testing is standard of care[30]. There have been some controversies regarding the methodology of *MGMT* testing, with some centers preferring pyrosequencing and others utilizing PCR. Immunohistochemistical assessment of *MGMT* does not appear to correlate with overall survival.[31]

Bevacizumab

Three uncontrolled studies indicate that the vascular endothelial growth factor (VEGF) antibody bevacizumab may have increased activity in elderly patients with glioblastoma.[32-34] In 2014, the efficacy of bevacizumab in newly diagnosed glioblastoma patients has been reported by two large, placebo-controlled, randomized trials.[35,36] The Avastin in Glioblastoma (AVAglio) phase III study evaluated the effect of the addition of bevacizumab to focal radiotherapy with concurrent TMZ, to the adjuvant component and then beyond the adjuvant component until progression.[34] Although improved progression-free survival (HR 0·65 (0·56–0·75)), preservation of baseline quality of life and performance status were reported, there was no improvement in

overall survival. Stratified by age over 70 years, the statistical significance with regards to PFS was lost [HR 0·78 (0·46–1·33)]; however this may reflect an issue of statistical power and small subgroups rather than a lack of clinical efficacy. The RTOG 0825 trial, sharing a similar design, also failed to demonstrate an overall survival benefit[35] but in contrast to the AVAglio study, a greater deterioration clinically assessed by patient reported outcome questionnaire, was evident in the bevacizumab group. There were differences in the design of these two studies that may influence determination of progression and patient reports outcomes. Radiological assessment in the RTOG 0825 study was by serial measurement of cross-sectional diameter and use of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST)[37] committee whereas the AVAglio study utilized an adaptation of the Macdonald criteria, similar to the newer RANO criteria, which takes into account the issues of pseudoprogression, pseudoresponse and changes in the non-enhancing disease.[38] Ongoing discussion and analyses may further clarify the apparent discordant results with regard to progression-free survival in these two pivotal trials.

No clinical or tissue based biomarkers have yet been prospectively shown to be associated with benefit from bevacizumab although patients with glioblastomas harbouring a proneural subtype may derive the most benefit.[39] At present bevacizumab has no role in the standard upfront treatment of glioblastoma; however, future clinical trials may attempt to target specific groups of patients defined by sets of biomarkers. The randomized Avastin plus Radiotherapy in Elderly Patients with Glioblastoma (ARTE) study, a phase II trial, will explore whether the addition of bevacizumab to radiotherapy improves outcome in elderly patients with newly diagnosed glioblastoma without *MGMT* promoter methylation (M. Weller, personal communication).

Symptomatic management

Glioblastoma can cause many difficult symptoms ranging from fatigue to those associated with raised intracranial pressure. Seizures may often occur as well as cognitive, motor or sensory deficits occurring in a location-dependent manner. Corticosteroids are often required to control symptoms of cerebral edema and their utility over time must be balanced with potential side effects such as proximal myopathy, steroid-induced diabetes, and osteoporotic fractures which can be debilitating. Furthermore, corticosteroids may reduce the benefit from TMZ in the most promising MGMT promoter methylated subgroup.[40] Anti-seizure medications are also often warranted. There is no randomised evidence pertaining to palliative care in the glioblastoma setting. However, based on a randomised study in non-small lung cancer, which demonstrated the addition of palliative care not only improved quality of life but also increased overall survival, many would advocate the early incorporation of palliative care support.[41]

Population-based retrospective studies

For glioblastoma, like many other cancers, results from randomized clinical trials (RCTs) may not reflect 'real world" outcomes as described in population based studies. Several large population based studies have shown that many elderly patients do not receive the 'gold standard' treatment. For example, despite the increasing body of evidence regarding the important benefit of resection rather than biopsy, numerous international pattern of care studies[42-46] demonstrate a much higher rate of biopsy alone rather than attempted resection in the elderly population.

The SEER database study published by Scott et. al. reported that among 2836 patients, only 46% of those over the age of 70 received both surgery and radiotherapy, with omission of

treatment associated with poorer survival.[19] A similar SEER study of 4,137 patients with glioblastoma, aged 65 or older, reported a median overall survival of 4 months and described age to be associated with lower odds of resection and provision of RT or chemotherapy.[19] The Princess Margaret Cancer Centre published outcomes of 131 patients aged greater than 70 treated in the 'temozolomide era' between 2004 and 2008.[47] Elderly patients were more likely to receive best supportive care or 'palliative' doses of radiotherapy with only 1 patient receiving 60Gy in 30 fractions in combination with TMZ. Only 6 patients (5%) received TMZ post-radiation, with only a median of 2.5 cycles administered. A retrospective review of 235 patients aged 65 or over treated between 2006 and 2013 at the Odette Cancer Center in Toronto provides a more contemporary overview regarding provision of care in the elderly setting.[48] With a median survival of approximately 2 months, 19% of patients were deemed not suitable for active treatment.

There is a likely another subgroup of elderly patients not reflected in statistics who might be presumptively diagnosed on radiological investigations (e.g. imaging for suspected stroke) but for various reasons (e.g. comorbidities, patient and family preference) do not proceed even to a biopsy. Of course, in certain scenarios, e.g. bedbound patient with dementia, it may be inappropriate to pursue active management.

Survivorship in the 'real world' would appear less favorable to that quoted in RCTs and may be a reflection of both physician preference to not to administer treatment in a group previously not studied as well as patient choice. The definition of 'elderly' varies across clinical trials and may appear to limit the ability to cross-compare data from these studies. That said, the NOA-08 trial had a median age of 72 (66-84) years in the TMZ arm and 72 (66-82) years in the RT arm. Age as a continuous variable or dichotomized at age 70 was not an independent

prognostic factor for either OS or event-free survival[13]; thus the association with age may not be as important in patients older than 70 years. Patients from population-based studies are clearly different that those included in the randomized trials. A patient-centered approach is important, as in all aspects of medicine, and treatment decisions need to involve a patient's own preferences and goals of care should be a focus early in the discussion regarding management.

Practical aspects:

Practical considerations such as performance status and even the ability of the patient to get to appointments can also come into play, as many of these patients are no longer driving. For example, a mobile elderly patient with a poor short-term memory, but with a strong family network advocating for active treatment, is far more likely to be treated than a socially isolated patient. If a cognitively intact patient with poor mobility is keen for treatment; again the presence of supportive family will often make a difference impacting on decision-making.

Often rehabilitation is not offered for glioblastoma patients postoperatively. However, there is evidence that postoperative rehabilitation in this setting is just as useful as in the stroke setting[49,50] and should be considered where possible. There are observational studies which show improvement in patients' functional status during the course of rehabilitation therapy, including the functional independence measure (FIM)[51,52] and referral for rehabilitation is advocated.[53]

Elderly patients and their caregivers may have numerous symptoms or challenges ahead. Challenges include treatment and tumor-related symptoms and deficits, seizures, headaches, communication difficulties (e.g. expressive or receptive aphasia), personality and behaviour changes (e.g. frontal syndrome with disinhibition and emotional lability), poor concentration, poor memory, fatigue, weakness, mobility; hemiparesis, impaired judgement/insight and

depression (reactive versus major). These challenges can be even more difficult to manage in the setting of comorbidities and polypharmacy often faced by elderly patients.

The clinical journey is a complex one and can involve interaction with many health professionals- including neurosurgeon, radiation oncologist (and radiation therapists), medical oncologist, palliative care physician, occupational therapist, physiotherapist, neurologist, endocrinologist (for steroid-induced diabetes) or diabetic educator, social worker, pharmacist, psychologist, speech pathologist etc. and ideally a cancer care coordinator should be available, where possible, to help the patient navigate through this difficult pathway.

Caregiver burnout is also very important for clinicians to be aware of. Recent studies have demonstrated that the global quality of life is often poorer in the caregiver than in the patients themselves.[54,55] Often, in the elderly setting, a spouse (if there is one) has their own co-morbidities to deal with and struggles to manage both physically and emotionally with the complexities involved with caring for a partner with glioblastoma.

Conclusion and recommendations

Selecting the appropriate treatment for an elderly patient with a newly diagnosed glioblastoma is challenging and a patient-centred approach is essential. Randomised evidence to guide treatment decisions is emerging (table 2) and there is less reason for nihilism. Initial consideration should include the appropriateness and extent of surgical intervention. With frailty and potential comorbidities there may be increased perioperative complications and prolonged recovery; however, maximal safe surgical resection should be considered. Subsequent management should incorporate initial symptomatic management including titration of corticosteroids and suitable anti-seizure medication if required. Early introduction of palliative

care may have a role in many patients. Management should be based upon the fitness of the patient, performance status, and *MGMT* promoter methylation status (Figure 2).[56] Standard radiotherapy of 60Gy in 30 fractions with concurrent and adjuvant TMZ can be utilized for most patients under the age of 70 and of appropriate fitness. In patients over the age of 70 there is evidence of efficacy for both radiotherapy alone and TMZ monotherapy respectively; the results of the NCIC-CTG/EORTC/TROG clinical trial will assess the benefit of hypofractionated radiotherapy with concurrent TMZ compared to radiotherapy alone. Most patients over 70 years of age appear not to benefit from conventional radiation schedules such as 60Gy in 30 fractions and a hypofractionated schedule is recommended. We acknowledge that some practitioners continue to recommend radical treatment (60Gy in 30 fractions with TMZ) for fit patients over the age of 70; however there are no randomized data to support this practice. *MGMT* may turn out to be even more important in the setting of elderly patients than in younger patients in terms of guiding management decisions. Ideally *MGMT* promoter methylation status should be determined on all patients 65 years and older. Patients lacking *MGMT* promoter methylation should be considered for a course of hypofractionated radiation therapy alone while those with methylated tumors may be offered temozolomide alone. Selection of these treatments requires an interdisciplinary discussion of the risks and benefits of RT versus TMZ, incorporation of the patient's own goals of care, and patient preference.

Some of the current algorithms for elderly glioblastoma patients are based on extrapolations from small and underpowered studies, but hopefully over the next few years, higher levels of evidence from larger maturing phase III studies will ensure future recommendations are more robust.

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Figure Legends

Figure 1: Overall Survival of Glioblastoma Patients Treated in Ontario, Canada Stratified by Decade of Age

Figure 2 Figure 2: Flow diagram of treatment considerations for elderly Glioblastoma patients (a) 65-70 and (b) >70

Table Legends

Table 1: Average age adjusted incidence per 100,000 and relative survival for GB stratified by age (CBTRUS)[2]

Table 2: Randomised clinical evidence for elderly glioblastoma patients.

Glioblastoma in the Elderly: Making Sense of the Evidence

Matthew Mason[1], Normand Laperriere[1], Wolfgang Wick[2], David A. Reardon[3], Annika Malmstrom[4], Elizabeth Hovey[5], Michael Weller[6] & James R Perry[7]

1) Department of Radiation Oncology, Princess Margaret Cancer Centre, University of Toronto, 610 University Avenue, Toronto, ON, M5T 2M9 Canada

2) Neurology Clinic & National Center for Tumor Disease and Neurology Clinic, Heidelberg University Medical Center & DKFZ, Heidelberg, Germany.

3) Center for Neuro-Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, Dana 2134, Boston, MA 02215-5450 USA

4) Department of Advanced Home Care and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

5) Department of Medical Oncology, Prince of Wales Hospital, Barker Street, Randwick NSW 2031 Australia

6) Department of Neurology, University Hospital Zurich, Frauenklinikstrasse 26, CH-8091 Zürich, Switzerland

7) Division of Neurology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, M4N 3M5 Canada

Running Title: Glioblastoma in the Elderly

Corresponding Author:
James Perry MD, FRCPC
Division of Neurology, Sunnybrook Health Sciences and Odette Cancer Centre,
A402, 2075 Bayview Avenue
University of Toronto, Toronto, Ontario, Canada
M4N 3M5
Ph: 416 480 4766
Fax: 416 480 5054
Email: James.Perry@sunnybrook.ca

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Abstract:

Glioblastoma is a highly malignant neoplasm, notorious for its poor prognosis. The median age of diagnosis is 64 years, with an increasing number of patients diagnosed over the age of seventy. Managing elderly patients with this condition is challenging. Management pathways may include surgery, radiotherapy (RT), chemotherapy and best supportive care (BSC). Many clinical trials in oncology exclude elderly patients, including some of those for malignant brain tumors leaving less evidence to guide treatment in the these patients. Recent advances in molecular diagnostics and biomarkers, such as 06-methylguanine-DNA-methyltransferase (*MGMT)* promoter methylation status, may help guide optimal treatment selection. Focusing on available randomized data, this review provides a practical overview of the evidence for the treatment of newly diagnosed glioblastoma in the elderly including management recommendations.

Keywords: Elderly, glioblastoma, surgery, radiotherapy, chemotherapy

Convention is to define the 'elderly' population as exceeding a specified chronological age which varies with temporal, geographical, social and cultural factors. Managing elderly patients can be challenging; medical comorbidities, multiple concomitant medications, and increasing fragility of health alter drug efficacy and the magnitude and spectrum of adverse effects related to treatment. With age, the natural insidious change of physiology and constitution affects pharmacokinetic processes with regards to absorption, metabolism, distribution and drug clearance.[1] Many clinical trials in oncology exclude elderly patients, including some of those for malignant brain tumors; as such there is less evidence to guide treatment in the elderly cohort. This review provides a practical overview of the evidence for the treatment of newly diagnosed glioblastoma in the elderly.

Epidemiology

Glioblastoma is a highly malignant neoplasm, notorious for its poor prognosis. The Central Brain Tumour Registry of the United States (CBTRUS) statistical report, which collates epidemiological data from over 50 state cancer registries, identified 112,458 malignant primary brain and central nervous system (CNS) tumors between 2006 and 2010 of which 45.2% were glioblastomas.[2] A median age of 64 at diagnosis and an average age-adjusted incidence rate per of 3·19 (3·16-3·21) per 100,000 were reported. Stratification by age detected an increase in incidence with age, and the peak rate of 14·93 in the 75-84 age range. Of note is the marked decrease in survival with advancing age (table 1). The 1-year and 2-year relative survival rates of

40·7% and 14·2% for patients aged 55-64 falls to 9·2% and 2·6% for patients aged 75 or older. An Ontario (Canada) population-based cohort study of all patients diagnosed with glioblastoma between 1982 and 1994 found poorer survival with respect to each increasing decade of age (Figure 1 courtesy of Paszat et. al. Unpublished 1999). Whether this poorer survival is a reflection of differing provisions of care based on chronological age or reflects more aggressive tumor biology, or both, is presently unclear.

The histologic hallmarks of glioblastoma, as defined by the World Health Organization (WHO), include cellular polymorphism, nuclear atypia, a high mitotic index, microvascular proliferation and necrosis.[3] With the emergence of personalized medicine, molecular diagnostics are increasingly used to improve the treatment and survival associated with glioblastoma. Prognostic biomarkers such as TP53 mutation, 1p deletion, cyclin dependent kinase (CDK) N2A/p16 deletion and epidermal growth factor receptor (EGFR) amplification vary with age[4]. In a histological review of 140 patients, *TP53* mutations and *EGFR* amplification had differing prognostic significance when stratifying by age, with TP53 mutations being positively prognostic for younger patients and negative for older patients (<70yrs 0.84; 95% CI 0.49 –1.42 versus >70yrs HR 7.54; 95% CI 2.38–23.87)[4]. Conversely *EGFR* amplification in the context of older patients was positively prognostic yet in younger patients it was negatively prognostic.[4]

More recently gene expression-based molecular analysis has been utilized to categorize glioblastoma into subtypes including proneural, neural, classical and mesenchymal subtypes.[5] Lee et al. performed a meta-analysis which substantiated the presence of these subtypes, as identified by genetic signature and suggested that the prognostic effect of age may in fact be a reflection of the differing prevalence of specific subtypes at differing ages; for example the

proneural subtype appears to occur more often in younger patients and is associated with longer survival.[6] Presently these markers do not have a defined role in clinical practice with regards to daily management decisions and remain under investigation. Of note, positive prognostic biomarkers, like mutations of *isocitrate dehydrogenase (IDH)* are virtually absent in glioblastoma of the elderly; similarly the general DNA methylation levels in the tumor tissue seem to be low. Despite this the frequency of *O6-Methylguanine-DNA methyltransferase (MGMT)* promoter methylation, itself an important positive predictive marker, does not vary with age.[7]

Surgery

In younger patients, maximal safe resection is advocated with the intent of preserving neurological function, providing maximal tissue for molecular profiling, and improving overall survival. Analysis of the extent of surgery in Radiation Therapy Oncology Group (RTOG) randomised trials, found significant improvement in survival with partial/total resection versus biopsy alone.[8] Review of an unselected population of 345 newly diagnosed glioblastoma patients from the German Glioma Network (GGN) demonstrated gross tumour resection to be associated with superior overall survival (OS) (median 17·1 months) compared to incomplete resection (median 11·7 months) and biopsy alone (median 8·7 months).[9] A multivariate analysis of 416 glioblastoma patients treated at a single institution between 1993 and 1999 reported resections of tumour volume in the order of 98% or greater to be associated with significant survival advantage (median survival 13 months, 95% CI 11·4–14·6 months versus 8·8 months (95% CI 7·4–10·2 months; $p < 0·0001$).[10]

There is one randomized trial pertaining to surgical intervention, including elderly patients with glioblastoma. This small study of 30 patients assessed the role of debulking surgery compared to biopsy alone.[11] Patients aged 65 or older with KPS >60 were randomized to open craniotomy and resection [14 patients with a median age of 70 (66-80)] or stereotactic biopsy [16 patients with a median of age 72 (67 -79)]. Surgical resection resulted in superior overall survival (171 days (95% CI 146–278) vs. 85 days (95% CI 55–157) p = 0·0346). More recently, a case-control study with a subgroup analysis of 52 patients aged 70 or over found a median survival of 4·5 months and 3 months for surgical resection and needle biopsy respectively (p = 0·03).[12] Perhaps the most relevant trial for the topic is the Neuro-oncology Working Group of the German Cancer Society NOA-08 study which found extent of surgery to be an independent prognostic factor for overall survival among glioblastoma patients 65 years and older.[13] Furthermore, multivariate analysis of all patients (n=342) participating in the Nordic trial of standard vs. hypofractionated radiotherapy vs. chemotherapy alone in newly diagnosed glioblastoma patients 65 years of age or older also demonstrated a survival benefit favoring surgery over biopsy alone (biopsy versus resection HR 1·50 (1·17 -1·92) p =0·001).[14]

Standard post-operative management for newly diagnosed glioblastoma

The European Organisation for Research and Treatment of Cancer (EORTC) 26981-22981/National Cancer Institute of Canada Clinical Trials Group (NCIC) CE.3 randomised phase III trial assessed the addition of temozolomide (TMZ) to radiotherapy (RT) in the concomitant and sequential adjuvant setting in glioblastoma patients aged 18-70.[15] Median age was 56 (range 19-71) and the selected population required Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. The addition of TMZ resulted in a median survival benefit of 2·5

months; 14·6 months (95% CI 13·2- 16·8) compared with 12·1 months (95%CI 11·2 -13·0) for radiotherapy alone. The 5-year analysis of this trial confirmed a persisting advantage and this has become the standard of care post-surgical resection for patients less than 70 years of age and of appropriate performance status.[16] In a recent review Laperriere et. al. noted that subgroup analysis of this trial demonstrated a trend to benefit in the more elderly subgroups, albeit with a less impressive hazard ratio and without reaching statistical significance. Specifically, there was diminishing benefit of combined treatment with increasing age (61-65 years: HR 0.64 p = 0.096 and 66–70 years: HR = 0·78 p = 0·34) compared to the overall group (HR 0·6, 95%CI 0·5-0·7; p<0·0001).[17] This may reflect less robust effects of the combined approach in the elderly or may be due to lower statistical power in the subgroup analysis.

Radiation for elderly patients

Randomized trials have long demonstrated a survival benefit from post-operative radiotherapy in the management of glioblastoma and more recently several trials have focused on the elderly. The French ANOCEF group found a median survival benefit of 12.2 weeks in favour of RT plus best supportive care (BSC) versus BSC alone.[18] Patients aged 70 or older with a KPS >70 and a diagnosis of glioblastoma or anaplastic astrocytoma were randomized postoperatively to receive BSC [(42 patients (median age 73; range 70-85)] or BSC and 50 Gy in 1.8 Gy fractions to a clinical target volume (CTV) consisting of enhancing tumour with a 2cm margin [(39 patients (median age 75; range 70-84)]. Overall survival was 16·9 (95% CI, 13·4 to 21·4) and 29·1 weeks (95% CI, 25·4 to 34·9) respectively. No significant difference was detected with regards to quality of life; however, Health Related Quality of Life (HRQoL) assessments were

incomplete. Cox proportional hazard modelling revealed that extent of surgery was associated with increased survival.

Scott et al. performed a large retrospective review of elderly glioblastoma patients diagnosed between 1993 and 2005.[19] The study sample of 2836 patients identified from the Surveillance, Epidemiology, and End Results (SEER) registry database had a median age of 76·9 years (range 71·0–98·0). Kaplan-Meier analysis revealed median cancer-specific survivals of 8 months for patients undergoing both surgery and postoperative radiotherapy, 4 months for radiation alone, 3 months for surgery alone and 2 months for neither surgery nor radiotherapy (log rank p<0·001). Multivariate analysis suggested radiotherapy significantly increased cancer-specific survival after adjusting for tumour size, tumour location, surgery and patient demographics with a hazard ratio (HR) of 0·43 (95% CI, 0·38–0·49). [19]

The biological effect of radiation on tumour and normal tissues is dependent upon the provision of dose over time as well as intrinsic radio-sensitivity (α) and repair capability (ß). Glioblastoma has an alpha-beta ratio (α/ ß) = 8Gy (5·0–10·8)[20] which is in the range of most tumours, while the alpha-beta ratio is approximately 2 for the normal central nervous system. As a result of this difference, hypofractionation reduces overall treatment time and may minimize the potential for tumor cell repopulation and provides a practical convenience for an elderly frail population. Roa et. al. randomized patients aged 60 or older to radiotherapy given as 60Gy in 30 fractions (47 patients, mean age 72.4 yrs, SD 5·4) or a hypofractionated regimen of 40Gy in 15 fractions (48 patients, mean 71·0 yrs, SD 5·5).[21] While this study was not sufficiently powered to conclude equivalence of these two fractionation schedules it suggested no significant differences in OS [median 5.1 months for the standard RT arm versus 5·6 months for the shorter course (log rank p = 0·57)], survival at 6 months (44·7% standard RT versus 41·7% hypofractionated RT),

or HRQoL. More patients required an increase of corticosteroid dose following the standard radiotherapy schedule compared to the hypofractionated course (p= 0·02).

The Nordic trial incorporated a different hypofractionated radiotherapy schedule.[14] There were 3 treatment arms including standard radiotherapy of 60Gy in 30 fractions, hypofractionated radiotherapy of 34Gy in 10 fractions or temozolomide 200mg/m2 days 1-5 every 28 days for up to 6 cycles. Standard radiotherapy (60Gy/30) was not routinely offered to elderly patients in some study sites so randomization between just the hypofractionated radiotherapy and temozolomide arms was permitted. Two hundred and ninety one glioblastoma patients (initially aged 60 years or older then in view of EORTC 26981-22981/NCIC-CTG CE.3 the age eligibility was adjusted so that patients 60-65 years old fit for combined treatment were excluded) were randomized to standard radiotherapy (n=100), hypofractionated radiotherapy (n=98) or temozolomide alone (n=93). A further 51 patients were randomized to either hypofractionated radiotherapy (n=25) or TMZ (n=26) by those centers that did not offer 60Gy in 30 fractions as their standard care.

The median age was 70 for both the hypofractionated and the standard radiotherapy groups. Median survival in the hypofractionated group was increased by 1·5 months compared to standard radiation in the three-arm comparison. Interestingly, on stratification by age, the advantage of hypofractionated radiation appeared better in patients over the age of 70 (7·0 (5·2–8·8) versus 5·2 (4·0–6·3) months). Treatment completion according to protocol was more frequent with the hypofractionated schedule (95% versus 72%). Salvage treatment was received for a similar proportion of patients in both groups while reported toxicity was not different between groups.

Temozolomide and O-6-methylguanine-DNA methyltransferase

The alkylating agent TMZ has activity in glioblastoma, and in combination with radiotherapy followed sequentially by a 6 month maintenance course represents the current standard of care for many patients. The mechanism of anti-tumour activity is believed to arise through methylation of DNA at the O-6 position of guanine by monomethyl-triazeno-imidazole-carboxyamide (MTIC), a non-enzymatic chemical degradation product of temozolomide.[22]

MGMT is a DNA repair protein implicated in resistance to alkylating agents.[23] Methylation of the *MGMT* promoter, located at 10q26, leads to suppression of *MGMT* gene expression and an increased likelihood of clinical benefit.[23-25] Hegi et al. assessed the *MGMT* promoter methylation status of patients randomized in the EORTC trial 26981/ NCIC CE.3 trial.[25] Regardless of treatment arm, OS was longer in patients with *MGMT* promoter methylation; 18.2 months compared with 12.2 months [HR for death 0·45 (95% CI 0·32 - 0·61)]. The magnitude of this effect was more substantial for patients receiving TMZ compared with those receiving radiation alone (P=0·007 vs. P=0·06, log-rank test). Of note, the majority of patients allocated to radiotherapy alone received alkylating agent chemotherapy as salvage treatment further supporting the use of concomitant therapy 'upfront' in newly diagnosed patients.[25] The prognostic significance of *MGMT* promoter methylation status was prospectively corroborated in the RTOG 0525 randomized study of TMZ dose density in the adjuvant setting. In this study, dose-dense TMZ (n=422) failed to demonstrate a survival advantage over standard dosing (n=411).[26] The absence of a TMZ-free control arm did not allow distinction between prognostic and predictive properties.

For elderly patients not suitable for the combined modality approach, recent evidence supports consideration of TMZ alone particularly for tumors harbouring *MGMT* promoter methylation.[27] Temozolomide alone was assessed in the Nordic study,[14] which found longer survival for both TMZ alone and hypofractionated radiotherapy over standard radiotherapy in patients older than 65 years of age. Comparison of TMZ and hypofractionated radiotherapy revealed no significant difference in overall survival (7·4 versus 8·4 months HR 0·82 95%CI 0·63-1·06). In the head to head comparison of TMZ versus hypofractionated radiation, 36% of the TMZ recipients had subsequent radiation and 29% of the hypofractionated group had salvage chemotherapy. *MGMT* promoter methylation status was available in 258 (75%) of 342 patients. Patients with *MGMT* promoter methylated tumors receiving TMZ survived 2.9 months longer than those with unmethylated tumors (HR 0·56, 95% CI 0·34-0·93, p=0·02). No survival advantage was identified based on *MGMT* promoter methylation status within the cohort receiving radiation (HR 0·97, 95% CI 0·69-1·38, p=0·81). Although the intent for the TMZ group was to complete six cycles, at least two cycles were administered to 86% of patients, and only 34% completed all six cycles. Haematological toxicity as well as nausea and vomiting were more frequent as would be expected in the TMZ cohort. In addition, a treatment-related death involving thrombocytopenia highlights that prescribing chemotherapy is not without the potential for serious toxicity.

In the NOA-08 study,[13] 192 patients received TMZ (1 week on, 1 week off schedule 100 mg/m2 days 1–7) and 178 patients received 60Gy radiotherapy alone over 6–7 weeks to the gross tumour volume (GTV) + 2 centimeters. Median overall survival was similar for the two treatment arms: 8·6 months in the TMZ group and 9·6 months in the radiotherapy group (HR

1·09, 95% CI 0·84–1·42, p non-inferiority=0·033). *MGMT* promoter methylation status was available in 55% of patients receiving TMZ and 57% of patients receiving radiation with a predictive benefit seen for patients receiving the alkylating agent in the context of *MGMT* promoter methylated tumors. Hematological toxicity, abnormal liver function tests, infections and thromboembolic events were more prevalent in the TMZ group.

These trials found that *MGMT* promoter methylation is a predictive biomarker of benefit from TMZ, but not radiotherapy. The randomized international NCIC/EORTC/TROG study, which completed accrual in September 2013 (JP, personal communication), aims to address the potential benefit of combining short course radiotherapy (40Gy in 15 fractions) with concurrent and adjuvant TMZ in patients over 65 years who have had prior surgery/biopsy at diagnosis and are not deemed suitable for the standard radiotherapy regimen of 60Gy.[28] MGMT status will be assessed in this study.

A phase 2 ANOCEF study suggests that older age and poor KPS should not preclude the use of TMZ alone.[29] This was a non-randomized study which recruited 70 patients with a median age of 77 (range 70-87) and a median KPS of 60 (range 30-60). Intriguingly this study found an improvement of KPS in excess of 10 for 23 (33%) of treated patients with 18 (26%) having a rise to 70 or more. A maximum of 12 cycles of TMZ was planned however the median number of cycles received was only 2 with 20% and 24% of patients having dose delays and dose reductions for hematological toxicity respectively. Grade 3 or 4 hematological toxicities were not insignificant with 13% experiencing grade 3-4 neutropenia and 14% grade 3-4 thrombocytopenia. No deaths were attributed to treatment. Although only 44% of patients were able to have tumor material assessed for *MGMT* promoter methylation, this study again

demonstrated its predictive role with a hazard ratio for death of 2.307(95% CI 1.073 to 4.962) for patients with unmethylated *MGMT* promoter status (P=0·03). This phase II study introduces the question – should more elderly patients with poor performance status be primarily treated with TMZ monotherapy? Or should TMZ monotherapy be employed only in those whose tumor harbors a methylated *MGMT* promoter?

Although *MGMT* promoter methylation status is increasingly available it still not used in all centres. In the future increasing evidence favoring MGMT testing is likely to demand more widespread availability; for example the European Association for Neuro-Oncology (EANO) guideline for the diagnosis and treatment of malignant gliomas has already declared that MGMT promoter methylation status testing is standard of care[30]. There have been some controversies regarding the methodology of *MGMT* testing, with some centers preferring pyrosequencing and others utilizing PCR. Immunohistochemistical assessment of *MGMT* does not appear to correlate with overall survival.[31]

Bevacizumab

Three uncontrolled studies indicate that the vascular endothelial growth factor (VEGF) antibody bevacizumab may have increased activity in elderly patients with glioblastoma.[32-34] In 2014, the efficacy of bevacizumab in newly diagnosed glioblastoma patients has been reported by two large, placebo-controlled, randomized trials.[35,36] The Avastin in Glioblastoma (AVAglio) phase III study evaluated the effect of the addition of bevacizumab to focal radiotherapy with concurrent TMZ, to the adjuvant component and then beyond the adjuvant component until progression.[34] Although improved progression-free survival (HR 0·65 (0·56–0·75)), preservation of baseline quality of life and performance status were reported, there was no improvement in

overall survival. Stratified by age over 70 years, the statistical significance with regards to PFS was lost [HR 0·78 (0·46–1·33)]; however this may reflect an issue of statistical power and small subgroups rather than a lack of clinical efficacy. The RTOG 0825 trial, sharing a similar design, also failed to demonstrate an overall survival benefit[35] but in contrast to the AVAglio study, a greater deterioration clinically assessed by patient reported outcome questionnaire, was evident in the bevacizumab group. There were differences in the design of these two studies that may influence determination of progression and patient reports outcomes. Radiological assessment in the RTOG 0825 study was by serial measurement of cross-sectional diameter and use of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST)[37] committee whereas the AVAglio study utilized an adaptation of the Macdonald criteria, similar to the newer RANO criteria, which takes into account the issues of pseudoprogression, pseudoresponse and changes in the non-enhancing disease.[38] Ongoing discussion and analyses may further clarify the apparent discordant results with regard to progression-free survival in these two pivotal trials.

No clinical or tissue based biomarkers have yet been prospectively shown to be associated with benefit from bevacizumab although patients with glioblastomas harbouring a proneural subtype may derive the most benefit.[39] At present bevacizumab has no role in the standard upfront treatment of glioblastoma; however, future clinical trials may attempt to target specific groups of patients defined by sets of biomarkers. The randomized Avastin plus Radiotherapy in Elderly Patients with Glioblastoma (ARTE) study, a phase II trial, will explore whether the addition of bevacizumab to radiotherapy improves outcome in elderly patients with newly diagnosed glioblastoma without *MGMT* promoter methylation (M. Weller, personal communication).

Symptomatic management

Glioblastoma can cause many difficult symptoms ranging from fatigue to those associated with raised intracranial pressure. Seizures may often occur as well as cognitive, motor or sensory deficits occurring in a location-dependent manner. Corticosteroids are often required to control symptoms of cerebral edema and their utility over time must be balanced with potential side effects such as proximal myopathy, steroid-induced diabetes, and osteoporotic fractures which can be debilitating. Furthermore, corticosteroids may reduce the benefit from TMZ in the most promising MGMT promoter methylated subgroup.[40] Anti-seizure medications are also often warranted. There is no randomised evidence pertaining to palliative care in the glioblastoma setting. However, based on a randomised study in non-small lung cancer, which demonstrated the addition of palliative care not only improved quality of life but also increased overall survival, many would advocate the early incorporation of palliative care support.[41]

Population-based retrospective studies

For glioblastoma, like many other cancers, results from randomized clinical trials (RCTs) may not reflect 'real world" outcomes as described in population based studies. Several large population based studies have shown that many elderly patients do not receive the 'gold standard' treatment. For example, despite the increasing body of evidence regarding the important benefit of resection rather than biopsy, numerous international pattern of care studies[42-46] demonstrate a much higher rate of biopsy alone rather than attempted resection in the elderly population.

The SEER database study published by Scott et. al. reported that among 2836 patients, only 46% of those over the age of 70 received both surgery and radiotherapy, with omission of

treatment associated with poorer survival.[19] A similar SEER study of 4,137 patients with glioblastoma, aged 65 or older, reported a median overall survival of 4 months and described age to be associated with lower odds of resection and provision of RT or chemotherapy.[19] The Princess Margaret Cancer Centre published outcomes of 131 patients aged greater than 70 treated in the 'temozolomide era' between 2004 and 2008.[47] Elderly patients were more likely to receive best supportive care or 'palliative' doses of radiotherapy with only 1 patient receiving 60Gy in 30 fractions in combination with TMZ. Only 6 patients (5%) received TMZ post-radiation, with only a median of 2.5 cycles administered. A retrospective review of 235 patients aged 65 or over treated between 2006 and 2013 at the Odette Cancer Center in Toronto provides a more contemporary overview regarding provision of care in the elderly setting.[48] With a median survival of approximately 2 months, 19% of patients were deemed not suitable for active treatment.

There is a likely another subgroup of elderly patients not reflected in statistics who might be presumptively diagnosed on radiological investigations (e.g. imaging for suspected stroke) but for various reasons (e.g. comorbidities, patient and family preference) do not proceed even to a biopsy. Of course, in certain scenarios, e.g. bedbound patient with dementia, it may be inappropriate to pursue active management.

Survivorship in the 'real world' would appear less favorable to that quoted in RCTs and may be a reflection of both physician preference to not to administer treatment in a group previously not studied as well as patient choice. The definition of 'elderly' varies across clinical trials and may appear to limit the ability to cross-compare data from these studies. That said, the NOA-08 trial had a median age of 72 (66-84) years in the TMZ arm and 72 (66-82) years in the RT arm. Age as a continuous variable or dichotomized at age 70 was not an independent

prognostic factor for either OS or event-free survival[13]; thus the association with age may not be as important in patients older than 70 years. Patients from population-based studies are clearly different that those included in the randomized trials. A patient-centered approach is important, as in all aspects of medicine, and treatment decisions need to involve a patient's own preferences and goals of care should be a focus early in the discussion regarding management.

Practical aspects:

Practical considerations such as performance status and even the ability of the patient to get to appointments can also come into play, as many of these patients are no longer driving. For example, a mobile elderly patient with a poor short-term memory, but with a strong family network advocating for active treatment, is far more likely to be treated than a socially isolated patient. If a cognitively intact patient with poor mobility is keen for treatment; again the presence of supportive family will often make a difference impacting on decision-making.

Often rehabilitation is not offered for glioblastoma patients postoperatively. However, there is evidence that postoperative rehabilitation in this setting is just as useful as in the stroke setting[49,50] and should be considered where possible. There are observational studies which show improvement in patients' functional status during the course of rehabilitation therapy, including the functional independence measure (FIM)[51,52] and referral for rehabilitation is advocated.[53]

Elderly patients and their caregivers may have numerous symptoms or challenges ahead. Challenges include treatment and tumor-related symptoms and deficits, seizures, headaches, communication difficulties (e.g. expressive or receptive aphasia), personality and behaviour changes (e.g. frontal syndrome with disinhibition and emotional lability), poor concentration, poor memory, fatigue, weakness, mobility; hemiparesis, impaired judgement/insight and

depression (reactive versus major). These challenges can be even more difficult to manage in the setting of comorbidities and polypharmacy often faced by elderly patients.

The clinical journey is a complex one and can involve interaction with many health professionals- including neurosurgeon, radiation oncologist (and radiation therapists), medical oncologist, palliative care physician, occupational therapist, physiotherapist, neurologist, endocrinologist (for steroid-induced diabetes) or diabetic educator, social worker, pharmacist, psychologist, speech pathologist etc. and ideally a cancer care coordinator should be available, where possible, to help the patient navigate through this difficult pathway.

Caregiver burnout is also very important for clinicians to be aware of. Recent studies have demonstrated that the global quality of life is often poorer in the caregiver than in the patients themselves.[54,55] Often, in the elderly setting, a spouse (if there is one) has their own co-morbidities to deal with and struggles to manage both physically and emotionally with the complexities involved with caring for a partner with glioblastoma.

Conclusion and recommendations

Selecting the appropriate treatment for an elderly patient with a newly diagnosed glioblastoma is challenging and a patient-centred approach is essential. Randomised evidence to guide treatment decisions is emerging (table 2) and there is less reason for nihilism. Initial consideration should include the appropriateness and extent of surgical intervention. With frailty and potential comorbidities there may be increased perioperative complications and prolonged recovery; however, maximal safe surgical resection should be considered. Subsequent management should incorporate initial symptomatic management including titration of corticosteroids and suitable anti-seizure medication if required. Early introduction of palliative

care may have a role in many patients. Management should be based upon the fitness of the patient, performance status, and *MGMT* promoter methylation status (Figure 2).[56] Standard radiotherapy of 60Gy in 30 fractions with concurrent and adjuvant TMZ can be utilized for most patients under the age of 70 and of appropriate fitness. In patients over the age of 70 there is evidence of efficacy for both radiotherapy alone and TMZ monotherapy respectively; the results of the NCIC-CTG/EORTC/TROG clinical trial will assess the benefit of hypofractionated radiotherapy with concurrent TMZ compared to radiotherapy alone. Most patients over 70 years of age appear not to benefit from conventional radiation schedules such as 60Gy in 30 fractions and a hypofractionated schedule is recommended. *MGMT* may turn out to be even more important in the setting of elderly patients than in younger patients in terms of guiding management decisions. Ideally *MGMT* promoter methylation status should be determined on all patients 65 years and older. Patients lacking *MGMT* promoter methylation should be considered for a course of hypofractionated radiation therapy alone while those with methylated tumors may be offered temozolomide alone. Selection of these treatments requires an interdisciplinary discussion of the risks and benefits of RT versus TMZ, incorporation of the patient's own goals of care, and patient preference.

Some of the current algorithms for elderly glioblastoma patients are based on extrapolations from small and underpowered studies, but hopefully over the next few years, higher levels of evidence from larger maturing phase III studies will ensure future recommendations are more robust.

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Figure Legends

Figure 1: Overall Survival of Glioblastoma Patients Treated in Ontario, Canada Stratified by Decade of Age

Figure 2 Figure 2: Flow diagram of treatment considerations for elderly Glioblastoma patients (a) 65-70 and (b) >70

Table Legends

Table 1: Average age adjusted incidence per 100,000 and relative survival for GB stratified by age (CBTRUS)[2]

Table 2: Randomised clinical evidence for elderly glioblastoma patients.

Glioblastoma in the Elderly: Making Sense of the Evidence

Matthew Mason[1], Normand Laperriere[1], Wolfgang Wick[2], David A. Reardon[3], Annika Malmstrom[4], Elizabeth Hovey[5], Michael Weller[6] & James R Perry[7]

1) Department of Radiation Oncology, Princess Margaret Cancer Centre, University of Toronto, 610 University Avenue, Toronto, ON, M5T 2M9 Canada

2) Neurology Clinic & National Center for Tumor Disease and Neurology Clinic, Heidelberg University Medical Center & DKFZ, Heidelberg, Germany.

3) Center for Neuro-Oncology, Dana-Farber Cancer Institute, 450 Brookline Ave, Dana 2134, Boston, MA 02215-5450 USA

4) Department of Advanced Home Care and Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden

5) Department of Medical Oncology, Prince of Wales Hospital, Barker Street, Randwick NSW 2031 Australia

6) Department of Neurology, University Hospital Zurich, Frauenklinikstrasse 26, CH-8091 Zürich, Switzerland

7) Division of Neurology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, M4N 3M5 Canada

Running Title: Glioblastoma in the Elderly

Corresponding Author:
James Perry MD, FRCPC
Division of Neurology, Sunnybrook Health Sciences and Odette Cancer Centre,
A402, 2075 Bayview Avenue
University of Toronto, Toronto, Ontario, Canada
M4N 3M5
Ph: 416 480 4766
Fax: 416 480 5054
Email: James.Perry@sunnybrook.ca

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Abstract:

Glioblastoma is a highly malignant neoplasm, notorious for its poor prognosis. The median age of diagnosis is 64 years, with an increasing number of patients diagnosed over the age of seventy. Managing elderly patients with this condition is challenging. Management pathways may include surgery, radiotherapy (RT), chemotherapy and best supportive care (BSC). Many clinical trials in oncology exclude elderly patients, including some of those for malignant brain tumors leaving less evidence to guide treatment in the these patients. Recent advances in molecular diagnostics and biomarkers, such as 06-methylguanine-DNA-methyltransferase (*MGMT)* promoter methylation status, may help guide optimal treatment selection. Focusing on available randomized data, this review provides a practical overview of the evidence for the treatment of newly diagnosed glioblastoma in the elderly including management recommendations.

Keywords: Elderly, glioblastoma, surgery, radiotherapy, chemotherapy

Convention is to define the 'elderly' population as exceeding a specified chronological age which varies with temporal, geographical, social and cultural factors. Managing elderly patients can be challenging; medical comorbidities, multiple concomitant medications, and increasing fragility of health alter drug efficacy and the magnitude and spectrum of adverse effects related to treatment. With age, the natural insidious change of physiology and constitution affects pharmacokinetic processes with regards to absorption, metabolism, distribution and drug clearance.[1] Many clinical trials in oncology exclude elderly patients, including some of those for malignant brain tumors; as such there is less evidence to guide treatment in the elderly cohort. This review provides a practical overview of the evidence for the treatment of newly diagnosed glioblastoma in the elderly.

Epidemiology

Glioblastoma is a highly malignant neoplasm, notorious for its poor prognosis. The Central Brain Tumour Registry of the United States (CBTRUS) statistical report, which collates epidemiological data from over 50 state cancer registries, identified 112,458 malignant primary brain and central nervous system (CNS) tumors between 2006 and 2010 of which 45.2% were glioblastomas.[2] A median age of 64 at diagnosis and an average age-adjusted incidence rate per of 3·19 (3·16-3·21) per 100,000 were reported. Stratification by age detected an increase in incidence with age, and the peak rate of 14·93 in the 75-84 age range. Of note is the marked decrease in survival with advancing age (table 1). The 1-year and 2-year relative survival rates of

40·7% and 14·2% for patients aged 55-64 falls to 9·2% and 2·6% for patients aged 75 or older. An Ontario (Canada) population-based cohort study of all patients diagnosed with glioblastoma between 1982 and 1994 found poorer survival with respect to each increasing decade of age (Figure 1 courtesy of Paszat et. al. Unpublished 1999). Whether this poorer survival is a reflection of differing provisions of care based on chronological age or reflects more aggressive tumor biology, or both, is presently unclear.

The histologic hallmarks of glioblastoma, as defined by the World Health Organization (WHO), include cellular polymorphism, nuclear atypia, a high mitotic index, microvascular proliferation and necrosis.[3] With the emergence of personalized medicine, molecular diagnostics are increasingly used to improve the treatment and survival associated with glioblastoma. Prognostic biomarkers such as TP53 mutation, 1p deletion, cyclin dependent kinase (CDK) N2A/p16 deletion and epidermal growth factor receptor (EGFR) amplification vary with age[4]. In a histological review of 140 patients, *TP53* mutations and *EGFR* amplification had differing prognostic significance when stratifying by age, with TP53 mutations being positively prognostic for younger patients and negative for older patients (<70yrs 0.84; 95% CI 0.49 –1.42 versus >70yrs HR 7.54; 95% CI 2.38–23.87)[4]. Conversely *EGFR* amplification in the context of older patients was positively prognostic yet in younger patients it was negatively prognostic.[4]

More recently gene expression-based molecular analysis has been utilized to categorize glioblastoma into subtypes including proneural, neural, classical and mesenchymal subtypes.[5] Lee et al. performed a meta-analysis which substantiated the presence of these subtypes, as identified by genetic signature and suggested that the prognostic effect of age may in fact be a reflection of the differing prevalence of specific subtypes at differing ages; for example the

proneural subtype appears to occur more often in younger patients and is associated with longer survival.[6] Presently these markers do not have a defined role in clinical practice with regards to daily management decisions and remain under investigation. Of note, positive prognostic biomarkers, like mutations of *isocitrate dehydrogenase (IDH)* are virtually absent in glioblastoma of the elderly; similarly the general DNA methylation levels in the tumor tissue seem to be low. Despite this the frequency of *O6-Methylguanine-DNA methyltransferase (MGMT)* promoter methylation, itself an important positive predictive marker, does not vary with age.[7]

Surgery

In younger patients, maximal safe resection is advocated with the intent of preserving neurological function, providing maximal tissue for molecular profiling, and improving overall survival. Analysis of the extent of surgery in Radiation Therapy Oncology Group (RTOG) randomised trials, found significant improvement in survival with partial/total resection versus biopsy alone.[8] Review of an unselected population of 345 newly diagnosed glioblastoma patients from the German Glioma Network (GGN) demonstrated gross tumour resection to be associated with superior overall survival (OS) (median 17·1 months) compared to incomplete resection (median 11·7 months) and biopsy alone (median 8·7 months).[9] A multivariate analysis of 416 glioblastoma patients treated at a single institution between 1993 and 1999 reported resections of tumour volume in the order of 98% or greater to be associated with significant survival advantage (median survival 13 months, 95% CI 11·4–14·6 months versus 8·8 months (95% CI 7·4–10·2 months; $p < 0·0001$).[10]

There is one randomized trial pertaining to surgical intervention, including elderly patients with glioblastoma. This small study of 30 patients assessed the role of debulking surgery compared to biopsy alone.[11] Patients aged 65 or older with KPS >60 were randomized to open craniotomy and resection [14 patients with a median age of 70 (66-80)] or stereotactic biopsy [16 patients with a median of age 72 (67 -79)]. Surgical resection resulted in superior overall survival (171 days (95% CI 146–278) vs. 85 days (95% CI 55–157) p = 0·0346). More recently, a case-control study with a subgroup analysis of 52 patients aged 70 or over found a median survival of 4·5 months and 3 months for surgical resection and needle biopsy respectively (p = 0·03).[12] Perhaps the most relevant trial for the topic is the Neuro-oncology Working Group of the German Cancer Society NOA-08 study which found extent of surgery to be an independent prognostic factor for overall survival among glioblastoma patients 65 years and older.[13] Furthermore, multivariate analysis of all patients (n=342) participating in the Nordic trial of standard vs. hypofractionated radiotherapy vs. chemotherapy alone in newly diagnosed glioblastoma patients 65 years of age or older also demonstrated a survival benefit favoring surgery over biopsy alone (biopsy versus resection HR 1·50 (1·17 -1·92) p =0·001).[14]

Standard post-operative management for newly diagnosed glioblastoma

The European Organisation for Research and Treatment of Cancer (EORTC) 26981-22981/National Cancer Institute of Canada Clinical Trials Group (NCIC) CE.3 randomised phase III trial assessed the addition of temozolomide (TMZ) to radiotherapy (RT) in the concomitant and sequential adjuvant setting in glioblastoma patients aged 18-70.[15] Median age was 56 (range 19-71) and the selected population required Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. The addition of TMZ resulted in a median survival benefit of 2·5

months; 14·6 months (95% CI 13·2- 16·8) compared with 12·1 months (95%CI 11·2 -13·0) for radiotherapy alone. The 5-year analysis of this trial confirmed a persisting advantage and this has become the standard of care post-surgical resection for patients less than 70 years of age and of appropriate performance status.[16] In a recent review Laperriere et. al. noted that subgroup analysis of this trial demonstrated a trend to benefit in the more elderly subgroups, albeit with a less impressive hazard ratio and without reaching statistical significance. Specifically, there was diminishing benefit of combined treatment with increasing age (61-65 years: HR 0.64 p = 0.096 and 66–70 years: HR = 0·78 p = 0·34) compared to the overall group (HR 0·6, 95%CI 0·5-0·7; p<0·0001).[17] This may reflect less robust effects of the combined approach in the elderly or may be due to lower statistical power in the subgroup analysis.

Radiation for elderly patients

Randomized trials have long demonstrated a survival benefit from post-operative radiotherapy in the management of glioblastoma and more recently several trials have focused on the elderly. The French ANOCEF group found a median survival benefit of 12.2 weeks in favour of RT plus best supportive care (BSC) versus BSC alone.[18] Patients aged 70 or older with a KPS >70 and a diagnosis of glioblastoma or anaplastic astrocytoma were randomized postoperatively to receive BSC [(42 patients (median age 73; range 70-85)] or BSC and 50 Gy in 1.8 Gy fractions to a clinical target volume (CTV) consisting of enhancing tumour with a 2cm margin [(39 patients (median age 75; range 70-84)]. Overall survival was 16·9 (95% CI, 13·4 to 21·4) and 29·1 weeks (95% CI, 25·4 to 34·9) respectively. No significant difference was detected with regards to quality of life; however, Health Related Quality of Life (HRQoL) assessments were

incomplete. Cox proportional hazard modelling revealed that extent of surgery was associated with increased survival.

Scott et al. performed a large retrospective review of elderly glioblastoma patients diagnosed between 1993 and 2005.[19] The study sample of 2836 patients identified from the Surveillance, Epidemiology, and End Results (SEER) registry database had a median age of 76·9 years (range 71·0–98·0). Kaplan-Meier analysis revealed median cancer-specific survivals of 8 months for patients undergoing both surgery and postoperative radiotherapy, 4 months for radiation alone, 3 months for surgery alone and 2 months for neither surgery nor radiotherapy (log rank p<0·001). Multivariate analysis suggested radiotherapy significantly increased cancer-specific survival after adjusting for tumour size, tumour location, surgery and patient demographics with a hazard ratio (HR) of 0·43 (95% CI, 0·38–0·49). [19]

The biological effect of radiation on tumour and normal tissues is dependent upon the provision of dose over time as well as intrinsic radio-sensitivity (α) and repair capability (ß). Glioblastoma has an alpha-beta ratio (α/ ß) = 8Gy (5·0–10·8)[20] which is in the range of most tumours, while the alpha-beta ratio is approximately 2 for the normal central nervous system. As a result of this difference, hypofractionation reduces overall treatment time and may minimize the potential for tumor cell repopulation and provides a practical convenience for an elderly frail population. Roa et. al. randomized patients aged 60 or older to radiotherapy given as 60Gy in 30 fractions (47 patients, mean age 72.4 yrs, SD 5·4) or a hypofractionated regimen of 40Gy in 15 fractions (48 patients, mean 71·0 yrs, SD 5·5).[21] While this study was not sufficiently powered to conclude equivalence of these two fractionation schedules it suggested no significant differences in OS [median 5.1 months for the standard RT arm versus 5·6 months for the shorter course (log rank p = 0·57)], survival at 6 months (44·7% standard RT versus 41·7% hypofractionated RT),

or HRQoL. More patients required an increase of corticosteroid dose following the standard radiotherapy schedule compared to the hypofractionated course (p= 0·02).

The Nordic trial incorporated a different hypofractionated radiotherapy schedule.[14] There were 3 treatment arms including standard radiotherapy of 60Gy in 30 fractions, hypofractionated radiotherapy of 34Gy in 10 fractions or temozolomide 200mg/m2 days 1-5 every 28 days for up to 6 cycles. Standard radiotherapy (60Gy/30) was not routinely offered to elderly patients in some study sites so randomization between just the hypofractionated radiotherapy and temozolomide arms was permitted. Two hundred and ninety one glioblastoma patients (initially aged 60 years or older then in view of EORTC 26981-22981/NCIC-CTG CE.3 the age eligibility was adjusted so that patients 60-65 years old fit for combined treatment were excluded) were randomized to standard radiotherapy (n=100), hypofractionated radiotherapy (n=98) or temozolomide alone (n=93). A further 51 patients were randomized to either hypofractionated radiotherapy (n=25) or TMZ (n=26) by those centers that did not offer 60Gy in 30 fractions as their standard care.

The median age was 70 for both the hypofractionated and the standard radiotherapy groups. Median survival in the hypofractionated group was increased by 1·5 months compared to standard radiation in the three-arm comparison. Interestingly, on stratification by age, the advantage of hypofractionated radiation appeared better in patients over the age of 70 (7·0 (5·2–8·8) versus 5·2 (4·0–6·3) months). Treatment completion according to protocol was more frequent with the hypofractionated schedule (95% versus 72%). Salvage treatment was received for a similar proportion of patients in both groups while reported toxicity was not different between groups.

Temozolomide and O-6-methylguanine-DNA methyltransferase

The alkylating agent TMZ has activity in glioblastoma, and in combination with radiotherapy followed sequentially by a 6 month maintenance course represents the current standard of care for many patients. The mechanism of anti-tumour activity is believed to arise through methylation of DNA at the O-6 position of guanine by monomethyl-triazeno-imidazole-carboxyamide (MTIC), a non-enzymatic chemical degradation product of temozolomide.[22]

MGMT is a DNA repair protein implicated in resistance to alkylating agents.[23] Methylation of the *MGMT* promoter, located at 10q26, leads to suppression of *MGMT* gene expression and an increased likelihood of clinical benefit.[23-25] Hegi et al. assessed the *MGMT* promoter methylation status of patients randomized in the EORTC trial 26981/ NCIC CE.3 trial.[25] Regardless of treatment arm, OS was longer in patients with *MGMT* promoter methylation; 18.2 months compared with 12.2 months [HR for death 0·45 (95% CI 0·32 - 0·61)]. The magnitude of this effect was more substantial for patients receiving TMZ compared with those receiving radiation alone (P=0·007 vs. P=0·06, log-rank test). Of note, the majority of patients allocated to radiotherapy alone received alkylating agent chemotherapy as salvage treatment further supporting the use of concomitant therapy 'upfront' in newly diagnosed patients.[25] The prognostic significance of *MGMT* promoter methylation status was prospectively corroborated in the RTOG 0525 randomized study of TMZ dose density in the adjuvant setting. In this study, dose-dense TMZ (n=422) failed to demonstrate a survival advantage over standard dosing (n=411).[26] The absence of a TMZ-free control arm did not allow distinction between prognostic and predictive properties.

For elderly patients not suitable for the combined modality approach, recent evidence supports consideration of TMZ alone particularly for tumors harbouring *MGMT* promoter methylation.[27] Temozolomide alone was assessed in the Nordic study,[14] which found longer survival for both TMZ alone and hypofractionated radiotherapy over standard radiotherapy in patients older than 65 years of age. Comparison of TMZ and hypofractionated radiotherapy revealed no significant difference in overall survival (7·4 versus 8·4 months HR 0·82 95%CI 0·63-1·06). In the head to head comparison of TMZ versus hypofractionated radiation, 36% of the TMZ recipients had subsequent radiation and 29% of the hypofractionated group had salvage chemotherapy. *MGMT* promoter methylation status was available in 258 (75%) of 342 patients. Patients with *MGMT* promoter methylated tumors receiving TMZ survived 2.9 months longer than those with unmethylated tumors (HR 0·56, 95% CI 0·34-0·93, p=0·02). No survival advantage was identified based on *MGMT* promoter methylation status within the cohort receiving radiation (HR 0·97, 95% CI 0·69-1·38, p=0·81). Although the intent for the TMZ group was to complete six cycles, at least two cycles were administered to 86% of patients, and only 34% completed all six cycles. Haematological toxicity as well as nausea and vomiting were more frequent as would be expected in the TMZ cohort. In addition, a treatment-related death involving thrombocytopenia highlights that prescribing chemotherapy is not without the potential for serious toxicity.

In the NOA-08 study,[13] 192 patients received TMZ (1 week on, 1 week off schedule 100 mg/m2 days 1–7) and 178 patients received 60Gy radiotherapy alone over 6–7 weeks to the gross tumour volume (GTV) + 2 centimeters. Median overall survival was similar for the two treatment arms: 8·6 months in the TMZ group and 9·6 months in the radiotherapy group (HR

1·09, 95% CI 0·84–1·42, p non-inferiority=0·033). *MGMT* promoter methylation status was available in 55% of patients receiving TMZ and 57% of patients receiving radiation with a predictive benefit seen for patients receiving the alkylating agent in the context of *MGMT* promoter methylated tumors. Hematological toxicity, abnormal liver function tests, infections and thromboembolic events were more prevalent in the TMZ group.

These trials found that *MGMT* promoter methylation is a predictive biomarker of benefit from TMZ, but not radiotherapy. The randomized international NCIC/EORTC/TROG study, which completed accrual in September 2013 (JP, personal communication), aims to address the potential benefit of combining short course radiotherapy (40Gy in 15 fractions) with concurrent and adjuvant TMZ in patients over 65 years who have had prior surgery/biopsy at diagnosis and are not deemed suitable for the standard radiotherapy regimen of 60Gy.[28] MGMT status will be assessed in this study.

A phase 2 ANOCEF study suggests that older age and poor KPS should not preclude the use of TMZ alone.[29] This was a non-randomized study which recruited 70 patients with a median age of 77 (range 70-87) and a median KPS of 60 (range 30-60). Intriguingly this study found an improvement of KPS in excess of 10 for 23 (33%) of treated patients with 18 (26%) having a rise to 70 or more. A maximum of 12 cycles of TMZ was planned however the median number of cycles received was only 2 with 20% and 24% of patients having dose delays and dose reductions for hematological toxicity respectively. Grade 3 or 4 hematological toxicities were not insignificant with 13% experiencing grade 3-4 neutropenia and 14% grade 3-4 thrombocytopenia. No deaths were attributed to treatment. Although only 44% of patients were able to have tumor material assessed for *MGMT* promoter methylation, this study again

demonstrated its predictive role with a hazard ratio for death of 2.307(95% CI 1.073 to 4.962) for patients with unmethylated *MGMT* promoter status (P=0·03). This phase II study introduces the question – should more elderly patients with poor performance status be primarily treated with TMZ monotherapy? Or should TMZ monotherapy be employed only in those whose tumor harbors a methylated *MGMT* promoter?

Although *MGMT* promoter methylation status is increasingly available it still not used in all centres. In the future increasing evidence favoring MGMT testing is likely to demand more widespread availability; for example the European Association for Neuro-Oncology (EANO) guideline for the diagnosis and treatment of malignant gliomas has already declared that MGMT promoter methylation status testing is standard of care[30]. There have been some controversies regarding the methodology of *MGMT* testing, with some centers preferring pyrosequencing and others utilizing PCR. Immunohistochemistical assessment of *MGMT* does not appear to correlate with overall survival.[31]

Bevacizumab

Three uncontrolled studies indicate that the vascular endothelial growth factor (VEGF) antibody bevacizumab may have increased activity in elderly patients with glioblastoma.[32-34] In 2014, the efficacy of bevacizumab in newly diagnosed glioblastoma patients has been reported by two large, placebo-controlled, randomized trials.[35,36] The Avastin in Glioblastoma (AVAglio) phase III study evaluated the effect of the addition of bevacizumab to focal radiotherapy with concurrent TMZ, to the adjuvant component and then beyond the adjuvant component until progression.[34] Although improved progression-free survival (HR 0·65 (0·56–0·75)), preservation of baseline quality of life and performance status were reported, there was no improvement in

overall survival. Stratified by age over 70 years, the statistical significance with regards to PFS was lost [HR 0·78 (0·46–1·33)]; however this may reflect an issue of statistical power and small subgroups rather than a lack of clinical efficacy. The RTOG 0825 trial, sharing a similar design, also failed to demonstrate an overall survival benefit[35] but in contrast to the AVAglio study, a greater deterioration clinically assessed by patient reported outcome questionnaire, was evident in the bevacizumab group. There were differences in the design of these two studies that may influence determination of progression and patient reports outcomes. Radiological assessment in the RTOG 0825 study was by serial measurement of cross-sectional diameter and use of the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST)[37] committee whereas the AVAglio study utilized an adaptation of the Macdonald criteria, similar to the newer RANO criteria, which takes into account the issues of pseudoprogression, pseudoresponse and changes in the non-enhancing disease.[38] Ongoing discussion and analyses may further clarify the apparent discordant results with regard to progression-free survival in these two pivotal trials.

No clinical or tissue based biomarkers have yet been prospectively shown to be associated with benefit from bevacizumab although patients with glioblastomas harbouring a proneural subtype may derive the most benefit.[39] At present bevacizumab has no role in the standard upfront treatment of glioblastoma; however, future clinical trials may attempt to target specific groups of patients defined by sets of biomarkers. The randomized Avastin plus Radiotherapy in Elderly Patients with Glioblastoma (ARTE) study, a phase II trial, will explore whether the addition of bevacizumab to radiotherapy improves outcome in elderly patients with newly diagnosed glioblastoma without *MGMT* promoter methylation (M. Weller, personal communication).

Symptomatic management

Glioblastoma can cause many difficult symptoms ranging from fatigue to those associated with raised intracranial pressure. Seizures may often occur as well as cognitive, motor or sensory deficits occurring in a location-dependent manner. Corticosteroids are often required to control symptoms of cerebral edema and their utility over time must be balanced with potential side effects such as proximal myopathy, steroid-induced diabetes, and osteoporotic fractures which can be debilitating. Furthermore, corticosteroids may reduce the benefit from TMZ in the most promising MGMT promoter methylated subgroup.[40] Anti-seizure medications are also often warranted. There is no randomised evidence pertaining to palliative care in the glioblastoma setting. However, based on a randomised study in non-small lung cancer, which demonstrated the addition of palliative care not only improved quality of life but also increased overall survival, many would advocate the early incorporation of palliative care support.[41]

Population-based retrospective studies

For glioblastoma, like many other cancers, results from randomized clinical trials (RCTs) may not reflect 'real world" outcomes as described in population based studies. Several large population based studies have shown that many elderly patients do not receive the 'gold standard' treatment. For example, despite the increasing body of evidence regarding the important benefit of resection rather than biopsy, numerous international pattern of care studies[42-46] demonstrate a much higher rate of biopsy alone rather than attempted resection in the elderly population.

The SEER database study published by Scott et. al. reported that among 2836 patients, only 46% of those over the age of 70 received both surgery and radiotherapy, with omission of

treatment associated with poorer survival.[19] A similar SEER study of 4,137 patients with glioblastoma, aged 65 or older, reported a median overall survival of 4 months and described age to be associated with lower odds of resection and provision of RT or chemotherapy.[19] The Princess Margaret Cancer Centre published outcomes of 131 patients aged greater than 70 treated in the 'temozolomide era' between 2004 and 2008.[47] Elderly patients were more likely to receive best supportive care or 'palliative' doses of radiotherapy with only 1 patient receiving 60Gy in 30 fractions in combination with TMZ. Only 6 patients (5%) received TMZ post-radiation, with only a median of 2.5 cycles administered. A retrospective review of 235 patients aged 65 or over treated between 2006 and 2013 at the Odette Cancer Center in Toronto provides a more contemporary overview regarding provision of care in the elderly setting.[48] With a median survival of approximately 2 months, 19% of patients were deemed not suitable for active treatment.

There is a likely another subgroup of elderly patients not reflected in statistics who might be presumptively diagnosed on radiological investigations (e.g. imaging for suspected stroke) but for various reasons (e.g. comorbidities, patient and family preference) do not proceed even to a biopsy. Of course, in certain scenarios, e.g. bedbound patient with dementia, it may be inappropriate to pursue active management.

Survivorship in the 'real world' would appear less favorable to that quoted in RCTs and may be a reflection of both physician preference to not to administer treatment in a group previously not studied as well as patient choice. The definition of 'elderly' varies across clinical trials and may appear to limit the ability to cross-compare data from these studies. That said, the NOA-08 trial had a median age of 72 (66-84) years in the TMZ arm and 72 (66-82) years in the RT arm. Age as a continuous variable or dichotomized at age 70 was not an independent

prognostic factor for either OS or event-free survival[13]; thus the association with age may not be as important in patients older than 70 years. Patients from population-based studies are clearly different that those included in the randomized trials. A patient-centered approach is important, as in all aspects of medicine, and treatment decisions need to involve a patient's own preferences and goals of care should be a focus early in the discussion regarding management.

Practical aspects:

Practical considerations such as performance status and even the ability of the patient to get to appointments can also come into play, as many of these patients are no longer driving. For example, a mobile elderly patient with a poor short-term memory, but with a strong family network advocating for active treatment, is far more likely to be treated than a socially isolated patient. If a cognitively intact patient with poor mobility is keen for treatment; again the presence of supportive family will often make a difference impacting on decision-making.

Often rehabilitation is not offered for glioblastoma patients postoperatively. However, there is evidence that postoperative rehabilitation in this setting is just as useful as in the stroke setting[49,50] and should be considered where possible. There are observational studies which show improvement in patients' functional status during the course of rehabilitation therapy, including the functional independence measure (FIM)[51,52] and referral for rehabilitation is advocated.[53]

Elderly patients and their caregivers may have numerous symptoms or challenges ahead. Challenges include treatment and tumor-related symptoms and deficits, seizures, headaches, communication difficulties (e.g. expressive or receptive aphasia), personality and behaviour changes (e.g. frontal syndrome with disinhibition and emotional lability), poor concentration, poor memory, fatigue, weakness, mobility; hemiparesis, impaired judgement/insight and

depression (reactive versus major). These challenges can be even more difficult to manage in the setting of comorbidities and polypharmacy often faced by elderly patients.

The clinical journey is a complex one and can involve interaction with many health professionals- including neurosurgeon, radiation oncologist (and radiation therapists), medical oncologist, palliative care physician, occupational therapist, physiotherapist, neurologist, endocrinologist (for steroid-induced diabetes) or diabetic educator, social worker, pharmacist, psychologist, speech pathologist etc. and ideally a cancer care coordinator should be available, where possible, to help the patient navigate through this difficult pathway.

Caregiver burnout is also very important for clinicians to be aware of. Recent studies have demonstrated that the global quality of life is often poorer in the caregiver than in the patients themselves.[54,55] Often, in the elderly setting, a spouse (if there is one) has their own co-morbidities to deal with and struggles to manage both physically and emotionally with the complexities involved with caring for a partner with glioblastoma.

Conclusion and recommendations

Selecting the appropriate treatment for an elderly patient with a newly diagnosed glioblastoma is challenging and a patient-centred approach is essential. Randomised evidence to guide treatment decisions is emerging (table 2) and there is less reason for nihilism. Initial consideration should include the appropriateness and extent of surgical intervention. With frailty and potential comorbidities there may be increased perioperative complications and prolonged recovery; however, maximal safe surgical resection should be considered. Subsequent management should incorporate initial symptomatic management including titration of corticosteroids and suitable anti-seizure medication if required. Early introduction of palliative

care may have a role in many patients. Management should be based upon the fitness of the patient, performance status, and *MGMT* promoter methylation status (Figure 2).[56] Standard radiotherapy of 60Gy in 30 fractions with concurrent and adjuvant TMZ can be utilized for most patients under the age of 70 and of appropriate fitness. In patients over the age of 70 there is evidence of efficacy for both radiotherapy alone and TMZ monotherapy respectively; the results of the NCIC-CTG/EORTC/TROG clinical trial will assess the benefit of hypofractionated radiotherapy with concurrent TMZ compared to radiotherapy alone. Most patients over 70 years of age appear not to benefit from conventional radiation schedules such as 60Gy in 30 fractions and a hypofractionated schedule is recommended. We acknowledge that some practitioners continue to recommend radical treatment (60Gy in 30 fractions with TMZ) for fit patients over the age of 70; however there are no randomized data to support this practice. *MGMT* may turn out to be even more important in the setting of elderly patients than in younger patients in terms of guiding management decisions. Ideally *MGMT* promoter methylation status should be determined on all patients 65 years and older. Patients lacking *MGMT* promoter methylation should be considered for a course of hypofractionated radiation therapy alone while those with methylated tumors may be offered temozolomide alone. Selection of these treatments requires an interdisciplinary discussion of the risks and benefits of RT versus TMZ, incorporation of the patient's own goals of care, and patient preference.

Some of the current algorithms for elderly glioblastoma patients are based on extrapolations from small and underpowered studies, but hopefully over the next few years, higher levels of evidence from larger maturing phase III studies will ensure future recommendations are more robust.

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Figure Legends

Figure 1: Overall Survival of Glioblastoma Patients Treated in Ontario, Canada Stratified by Decade of Age

Figure 2 Figure 2: Flow diagram of treatment considerations for elderly Glioblastoma patients (a) 65-70 and (b) >70

Table Legends

Table 1: Average age adjusted incidence per 100,000 and relative survival for GB stratified by age (CBTRUS)[2]

Table 2: Randomised clinical evidence for elderly glioblastoma patients.

Table 1
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Table 1: Average age adjusted incidence per 100,000 and relative survival for GB stratified by age (CBTRUS)(2)

Age (years)	Average age adjusted incidence per 100,000	1yr Relative Survival	2yr Relative survival	5yr Relative survival
45-54	3.62	52.7%	20.8%	5.9%
55-64	8.08	40.7%	14.2%	3.8%
65-74	13.09	23.7%	7.2%	1.7%
75-84	14.93	9.2% (≥75)	2.6% (≥75)	0.8% (≥75)
≥85	9.24			

Table 2
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Table 2: Randomised clinical evidence for elderly GB patients.

Title	Treatment Arm	Number of patients	Age Median (Range)	Outcome
Debulking or biopsy of malignant glioma in elderly people – a randomized study[11]	Stereotactic biopsy Open Craniotomy/ Resection	16 14	72 (67-79) 70 (66 – 80)	85 days (95% CI 55–157) 171 days (95% CI 146–278) (p = 0.035)
Radiotherapy for Glioblastoma in the Elderly[18]	Best Supportive Care (BSC) Radiotherapy 50Gy in 28 fractions with BSC	42 39	73 (70 -85) 75 (70-84)	16.9 weeks (95% CI, 13.4 to 21.4) 29.1 weeks (95% CI, 25.4 to 34.9) HR for death in RT Group 0.47 (95%CI 0.29 to 0.76; p = 0.002 by the log-rank test)
Abbreviated Course of Radiation Therapy in Older Patients With Glioblastoma Multiforme: A Prospective Randomized Clinical Trial [21]	Standard radiotherapy (60·0 Gy in 2·0 Gy fractions over 6 weeks) Short-course regimen (40 Gy in 15 fractions over 3 weeks)	47 48	Mean 72.4 (SD 5.4) Mean 71 (SD 5.5)	Median survival 5.1 months Median survival 5.6 months (HR 0.89; 95% CI, 0.59 to 1.36; p = .57)
Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in	Temozolomide alone 100 mg/m ^{2} given on days 1–7 of 1 week every 14 days	195	72 (66–84)	8.6 months(95% CI 7.3–10.2)

the elderly: the NOA-08 randomised, phase 3 trial[13]	Radiotherapy 60·0 Gy, administered over 6–7 weeks in 30 fractions of 1·8–2·0 Gy	178	71 (66–82)	9.6 months (8.2–10.8) (HR 1·09, 95% CI 0·84–1·42, $p_{\text{non inferiority}}$=0·033)
Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial[14]	Standard radiotherapy (60·0 Gy in 2·0 Gy fractions over 6 weeks)	100	70 years (60–80)	6·0 months (95% CI 5·1-6·8)
	Hypofractionated radiotherapy (34·0 Gy in 3·4 Gy fractions over 2 weeks	98	70 (60–83)	7·5 months (95% CI 6·5-8·6)
	Temozolomide (200 mg/m^2 on days 1-5 of every 28 days for up to six cycles)	93	70 (60–88)	8·3 months (95% CI 7·1-9·5)

Figure 1
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Figure 1: Overall Survival of Glioblastoma Patients Treated in Ontario, Canada Stratified by Decade of Age

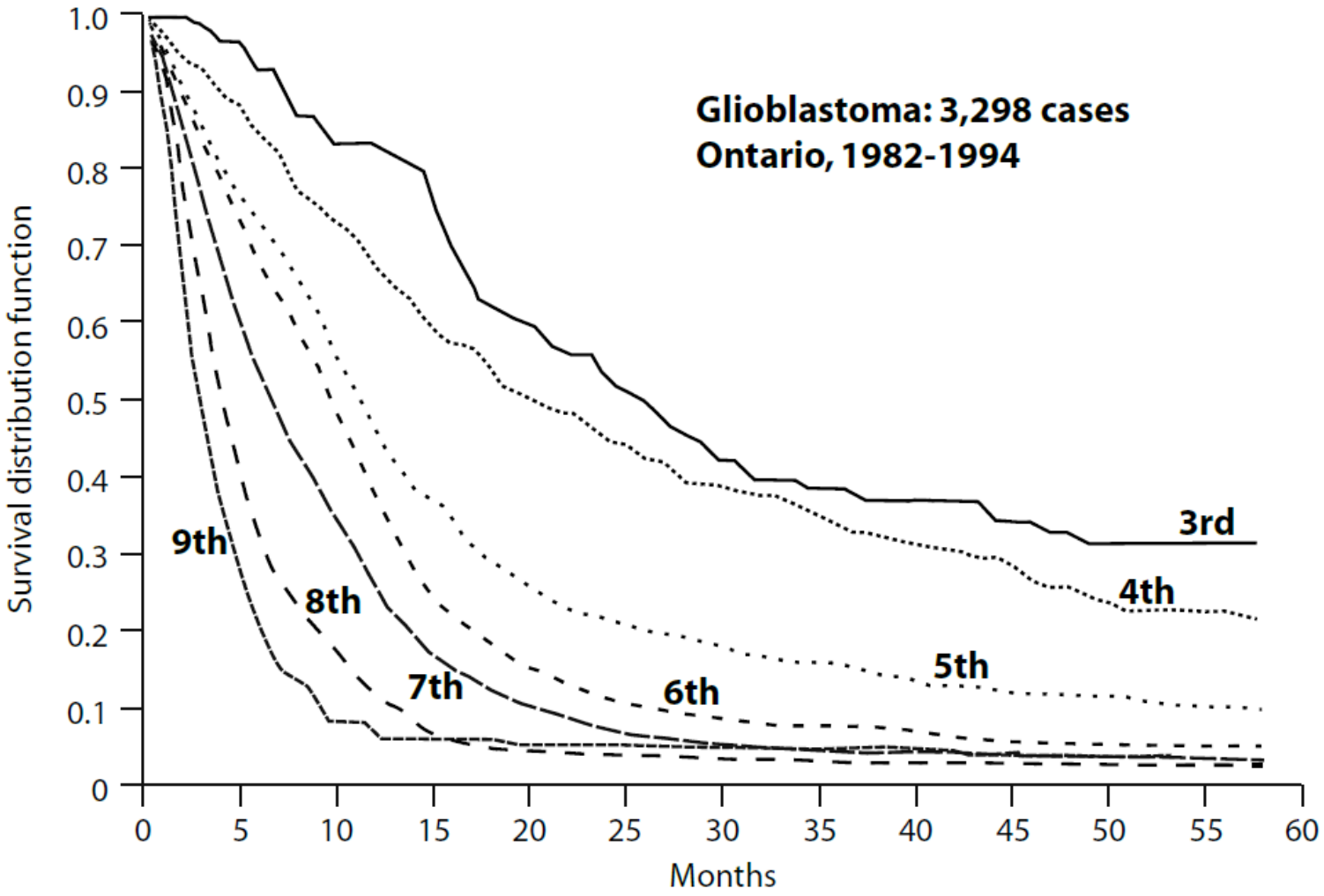

Figure 2

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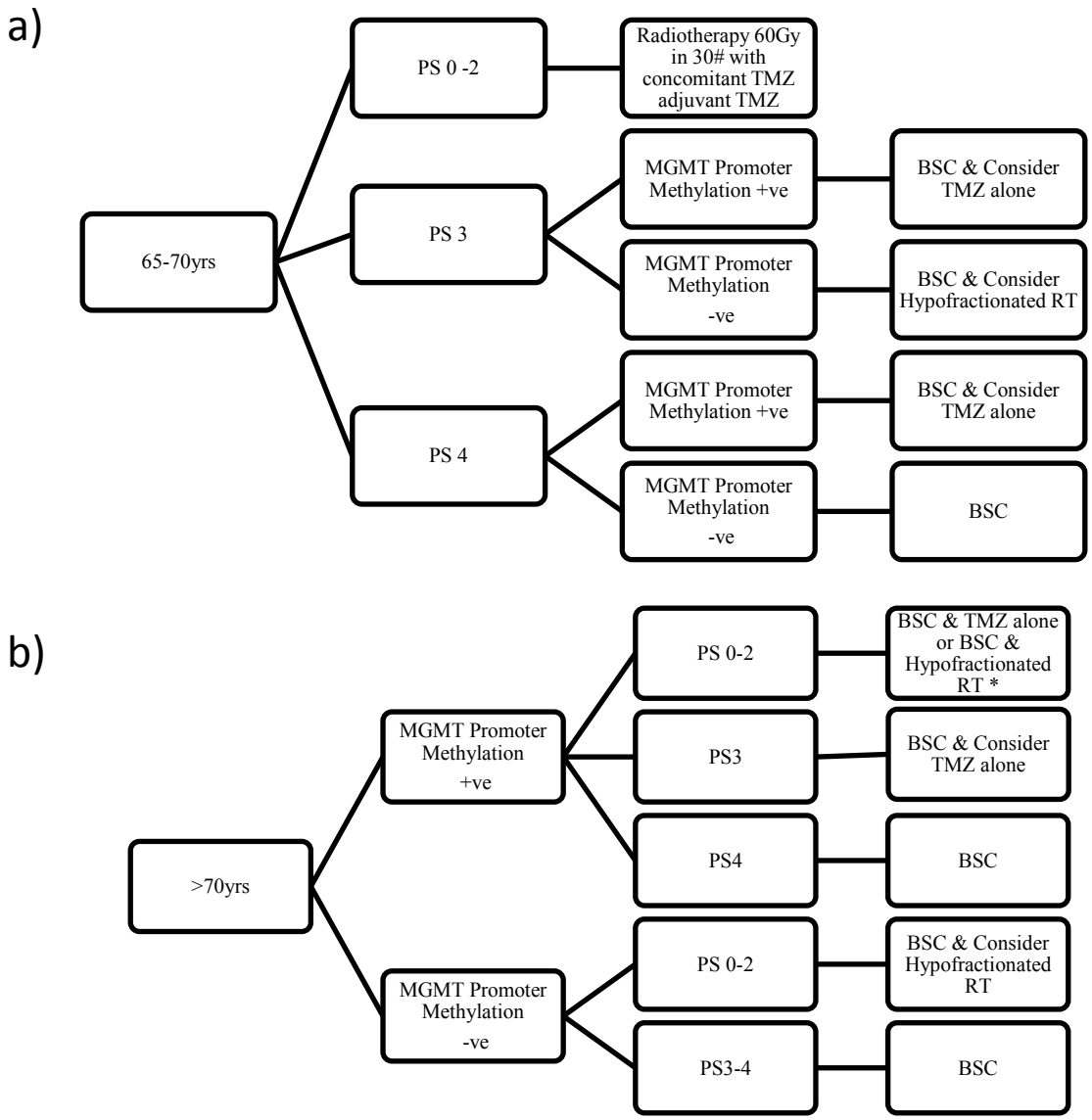
Figure 2: Flow diagram of treatment considerations for elderly Glioblastoma patients (a) 65-70 and (b) >70



*Outcome awaited of NCIC CTG CE6